

M₂₀₁₅

THE EFFECT OF *QÌGŌNG* IN NATURAL KILLER CELLS IN COLO-RECTAL CANCER PATIENTS UNDERGOING CHEMOTHERAPY

A CLINICAL RESEARCH PROTOCOL

SARA PATRÍCIA CARVALHO COSTA
DISSERTAÇÃO DE MESTRADO APRESENTADA
AO INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR
DA UNIVERSIDADE DO PORTO EM
MEDICINA TRADICIONAL CHINESA

SARA PATRÍCIA CARVALHO COSTA

THE EFFECT OF *QÌGŌNG* IN NATURAL KILLER CELLS IN COLO-RECTAL CANCER PATIENTS UNDERGOING CHEMOTHERAPY

A Clinical Research Protocol

Dissertação de Candidatura ao Grau de Mestre em Medicina Tradicional Chinesa submetida ao Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto.

Orientador - Prof. Doutor António Araújo

Categoria - Assistente Graduado e Director do Serviço de Oncologia Médica do Centro Hospitalar do Porto; Professor Auxiliar Convidado do Instituto de Ciências Biomédicas Abel Salazar.

Afiliação - Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto.

Co-Orientador – Prof. Doutor Henry J. Greten

Categoria – Professor Associado

Afiliação – Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto.

Co-Orientador – Mestre Mário J. Gonçalves

Categoria – Especialista em *Qìgōng*

Afiliação – Heidelberg School of Chinese Medicine

Co-Orientador – Prof. Doutor Jorge Machado

Categoria – Professor Associado

Afiliação – Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto

Resumo

Introdução: Tendo por base a revisão de vários estudos científicos reconhece-se uma relação entre o cancro e o sistema imunitário – Teoria da Imunoedição. O fenótipo imunológico do tumor é continuamente moldado por factores ambientais e emocionais que provocam variações do sistema neurológico e endócrino.

As células NK têm um papel crucial no sistema de imuno vigilância do cancro. Baixos níveis circulantes destas células têm sido relacionados com o efeito auxiliador na terapêutica do cancro, nomeadamente cancro colo-rectal (CCR).

De acordo com Chen (2002), *Qigōng* tem a capacidade de estimular o funcionamento do sistema imunitário actuando na microcirculação e no aporte de oxigénio às células que actuam no sistema imunitário até ao local do tumor.

Qigōng define-se como um *biofeedback vegetative* actuando no sistema nervoso central provocando uma resposta de relaxamento fisiológico uma vez que activa o sistema autónomo parassimpático. Esta teoria é fundamentada pelos novos conhecimentos da psiconeuroimunologia.

O uso combinado de exercícios físicos com a respiração e a meditação ajuda a harmonizar as funções fisiológicas do corpo, da mente e do espírito.

Alguns estudos relacionados com os modelos da psicologia relatam a interacção entre o *Qigōng* e o sistema nervoso somático e autónomo ajudando no controlo dos efeitos secundários do tratamento do cancro como das emoções, o cansaço e nas náuseas

Objectivos: 1) Avaliar os efeitos de um esquema de exercícios de *Qigōng* designados por "*Happy Qigōng*" no sistema imunológico, especificamente nas células NK em doente com CCR; 2) Relacionar o *status* psicoemocional dos pacientes com cancro, quando tratados com a terapia de *Qigōng*, com a melhoria da qualidade de vida bem como com a estimulação do seu sistema imunitário.

Métodos: Os pacientes serão recrutados no serviço de Oncologia no Centro Hospitalar do Porto – Hospital de S. António. Os critérios de inclusão serão: paciente com CCR operados a fazer quimioterapia, idade >18 anos e com capacidade de assinar o consentimento informado. Os pacientes serão excluídos se: estiverem a usar factores estimulantes de colónias.

Os pacientes serão randomizados em três grupos: grupo do *Qigōng* verdadeiro (n=10); grupo do *Qigōng* placebo (n=10) e o grupo controlo (n=10).

Inicialmente todos os sujeitos serão avaliados em linha de base (T0) recolhendo uma amostra sanguínea para avaliação das células NK e preencherão questionários

sociodemográficos, de avaliação da qualidade de vida e ansiedade e depressão. O estudo terá a duração de três semanas.

Será recolhida uma análise sanguínea por profissional de saúde qualificado no primeiro dia após inclusão do paciente no estudo, uma segunda recolha será realizada no 16º dia do estudo e uma terceira recolha será realizada no 23º dia do estudo.

O grupo do *Qigōng* verdadeiro receberá 6 sessões de terapia com *Qigōng*, duas vezes por semana entre as quimioterapias. Será recolhida uma análise sanguínea da seguinte forma: antes de começar o protocolo de exercícios de *Qigōng* (T0); durante a segunda semana de realização do protocolo (T1) e após ter terminado todas as sessões do protocolo (T2).

O grupo do *Qigōng* placebo fará o mesmo procedimento que o grupo do verdadeiro *Qigōng* mudando apenas o protocolo de exercícios de *Qigōng*.

O grupo controlo apenas colherá as amostras de sangue não fazendo o protocolo de exercícios de *Qigōng*.

Intervenção: O grupo do verdadeiro *Qigōng* receberá treino com o protocolo de exercícios do “*Happy Qigōng*” 2x/semana. O grupo do placebo *Qigōng* apenas fará a posição de *Standing* enquanto assiste a um programa de televisão do agrado do paciente.

Ambos os grupos serão aconselhados a repetir os exercícios todos os dias.

Conclusão: Baseado em alguns conceitos teóricos e em estudos anteriores pretende-se verificar:

- O aumento da actividade do sistema imunitário, mais especificamente o aumento das células NK.
- O valor clínico do *Qigōng* no tratamento de pacientes com CCR.
- O aumento da qualidade de vida dos doentes com cancro.
- Avaliação dos custos-eficácia nos sistemas de saúde.

Palavras-chave: Medicina tradicional chinesa, *Qigōng*, cancro colo-rectal, efeito do *Qigōng* no sistema imunitário, células NK, efeito do *Qigōng* na qualidade de vida do doente.

Abstract

Background: Several studies have demonstrated the highly relation between the cancer and the modulation of the immune system recognized the existence of a highly complex relationship between cancer and the immune system - immunoediting theory - this theory tell us that the immunogenic phenotype of the tumor can be frequently shaped by immunological factor. Cells like NK-cells are associated with immune-surveillance and their low levels in the human body are now related with a helper effect in cancer therapy, specially the colorectal cancer. Accordingly to Chen (2002), *Qigōng* produces an increase in the immune response, which may enhance the immune deficiency experienced by most of cancer patients and the increase of the microcirculatory functions.

Qigōng is a vegetative biofeedback therapy that acts in *the* central nervous system and causes a physiological relaxation response according to the new knowledge related on psychoneuroimmunology theory. The combined use of physical exercise and meditation serves to harmonize body, mind and spirit. Some physiologic models propose that *Qigōng* have biomechanical effects such as in the immune system and in the autonomic and somatic nervous system, helping in the emotional control, fatigue and nausea.

Objectives: 1) Evaluate the effect of *Qigōng* (“Happy *Qigōng*”) on the immune system, specifically in NK cells in colo-rectal cancer (CRC); 2) Correlate the effect of *Qigōng* on the immune system with patient’s psychoemotional status as well as is quality of life.

Methods: Patients will be recruited in the Oncology Center of Centro Hospitalar do Porto – Hospital de S. António. According to the following inclusion criteria: patients with CRC after have done surgery and now undergoing chemotherapy, age >18 years old, ability to give informed consent; no use of Colony Stimulating Factors (CSF). Patients will be randomized in three groups: true *Qigōng* group (n=10); the placebo *Qigōng* group (n=10) and the control group (n=10). The true *Qigōng* group will receive 6 sessions of *Qigōng* therapy, twice a week between the chemotherapy protocol. Blood samples will be collect at baseline (T0) on the day prior to do *Qigōng* and the following samples will be collect in the second week after starting the *Qigōng* protocol (T1) and in the end of the *Qigōng* protocol (T2). The placebo *Qigōng* group will do the same protocol of the *verum Qigōng* group but not doing the real form of *Qigōng*. The control group only will collect the blood sampling for the study without receiving any *Qigōng* treatment.

Intervention: The true *Qigōng* group will receive training exercises with the “Happy *Qigōng*” protocol 2x/week. The placebo group (placebo *Qigōng*) will consist of a “standing” position while watching a television program of their choice.

Both groups will be encouraged to repeat the exercises daily at home.

Expected Results: Based on previous study and theoretical considerations, this study looks for:

- Confirm an improvement in immune status and more specifically in NK cells.
- Clinical value of *Qìgōng* in treatment colo-rectal cancer patients.
- Improvement of quality of life in the patients with cancer.
- Evaluation cost-effectiveness from health-care systems.

Key words: Traditional Chinese Medicine, *Qìgōng*, colo-rectal cancer, *Qìgōng* effects in Immunology, NK cells, *Qìgōng* and the Quality of Life.

Dedication

To love.

Only love is able to heal.

To all, who suffer, with cancer pathology.

Acknowledgements

I would like to start thanking to the people who I love for the comfort in good and bad times.

To my closest family and friends, for all their love and background support in my life.

To all my friends who didn't believe in that project they gave me the strength that I needed to continue without connecting to setbacks.

To my dears Professors Johannes Greten, Mário Gonçalves and Jorge Machado, for all the knowledge transmitted and constant enthusiastic and support that contributed to my development as a person.

To Professor Doutor António Araújo (Department of Oncology in Centro Hospitalar do Porto - Hospital de S. António) for his sympathy, support and contribution in this project.

To Maria João Santos, for her support and love for TCM (Traditional Chinese Medicine) and research, that allowed the execution of this master thesis and for the friendship and understanding in my outpourings.

To Petra for her support in general management.

Finally, to the few people, who have crossed in my life and allowed me to open my mind and my spirit for the great mystery that is to exist.

Abbreviations

ACF	Aberrant Crypt Foci	IARC	International Agency for Research on Cancer
ACP	Adenomatous polyposis coli	IBD	Inflammatory Bowel Disease
AJCC	American Joint Committee on Cancer	IFN	Interferons
ALT	Algor Laedens Theory	IFN- γ	Interferons gamma
APC	Adenomatous Polyposis Coli	IgG	Immunoglobulin G
APC/ β	APC/ β – catenin	IgA	Immunoglobulin A
BC	Before Christ	IgM	Immunoglobulin M
CAM	Complementary and Alternative Medicine	IL	InterleuKin
CBT-I	Cognitive Behavioural Therapy for Insomnia	IL-1	InterleuKin 1
CC	Chemokine	IL-10	InterleuKin 10
CCR	Cancro Colo-rectal	IL-13	InterleuKin 13
CRC	Colo-rectal cancer	IL-2	InterleuKin 2
CD3	cluster of differentiation 3	IL-4	InterleuKin 4
CD4	cluster of differentiation 4	IL-5	InterleuKin 5
CD56	cluster of differentiation 56	IL-6	InterleuKin 6
CD8	cluster of differentiation 8	K-ras	Kirsten rat sarcoma viral oncogene homolog
CRC	Colo-Rectal Cancer	LAI	Adherence Inhibition
CSF	Cerebrospinal fluid	LAK	Lymphokine Activated Killer
DNA	Deoxyribonucleic acid	MADH2	Mothers against decapentaplegic homolog 2
DCC	Deleted in Colorectal Carcinoma	MADH4	Mothers against decapentaplegic homolog 4
FAP	Familial Adenomatous Polyposis	MHC	Major Histocompatibility Complex
GC	Guiding Criteria	MLT	Melatonin
GTF	Growth Tumor Factor	MQ	Medical Qìgōng
HNPCC	Hereditary No-Polyposis Colon Cancer	mRNA	Hypothalamicmessenger RNA
HPA	Hypothalamus-Pituitary-Adrenal	MSI	Microsatellite Instability

NFK β	factor nuclear kappa B	T1	Tempo 1
NK	Natural Killer	T2	Tempo 2
NKG2D	natural-killer group 2, member D	TCM	Traditional Chinese Medicine
PMNs	Polymorph nuclear cells	TFN	Tumor Factor Necrosis
PNI	Psychoneuroimmunology	Th1	T helper cells 1
QOL	Quality of life	Th2	T helper cells 2
SPSS	Statistical Package for Social Sciences	TNF- α	Tumor-Necrosis-Factor alfa
T0	Baseline	TP53	tumor protein p53
		WHO	World Health Organization
		5- FU	5-Fluorouracil

Index

Resumo	III
Abstract	V
Dedication	VII
Acknowledgements	VIII
Abbreviations	9
Index	11
Illustrations Index	13
Tables Index	13
Introduction	15
Chapter I – Literature Review	16
1. Colorectal Cancer Overview	16
1.1.Epidemiology and Etiopathophysiology	16
1.2.CRC Clinical Presentation and Staging	20
1.3.Risk factors	23
1.4.Diagnose of CRC	25
1.5.Treatment and Chemotherapy of CRC	26
2. Immunology	30
2.1.Immunologic System	30
2.2.NK Cells	33
2.3.Cancer and natural killer cells	34
2.4.CRC and Immunologic System	35
2.5.Psychoneuroimmunology and Cancer	36
3. Traditional Chinese Medicine	41
3.1.Heidelberg Model of Chinese Medicine	43
3.2.Diagnosis according to the Heidelberg Model of TCM	44
3.3.Chinese Medicine and Cancer	47
3.4.Qìgōng – An Historical Overview	53
3.5.Qìgōng Definition	55
3.6.Nowadays Qìgōng	56
Chapter II – Study Methodology	64
1.Study design	64
1.1 Investigation question and aim of the study	64
1.2.Objectives	64
1.3.Hypothesis of study	65
2.Methods	65
2.1.Recruitment	65

2.1.1.Inclusion criteria	65
2.1.2.Exclusion criteria	66
3.Measurements	66
3.1.Main parameters	66
3.2.Secondary endpoints	66
3.3.Experimental protocol	67
3.3.Statistical analysis	68
4.Intervention	68
4.1. <i>Verum</i> Group	68
4.2. <i>Sham</i> group	69
4.3.Control group	69
5.Qìgōng exercises and their explanation	70
6.Ethical Consideration	75
7.Expected Results	76
8.Conclusion	77
9.References	78
Anexos	84

Illustrations Index

Figure 1: Molecular model of adenocarcinoma sequence.	19
Figure 2: TNM Classification System.	22
Figure 3: Immune system types of cells.	31
Figure 4: The division of the Lymphoid stem cell.	32
Figure 5: Phychoneuroendocrine regulation system.	38
Figure 6: Limbic system explanation.	39
Figure 7: Compass Rose representing the five elements theory.	42
Figure 8: Schematic representation the methodology of diagnosis in TCM.	45
Figure 9: The Heidelberg Model of TCM.	46
Figure 10: TCM recognize that the human being functions as a body-mind network.	48
Figure 11: Mechanism of cancer disease according to MTC theory.	50
Figure 12: Representative scheme of the Man between heaven and earth.	71
Figure 13: R1 point (Fons Scatens).	71
Figure 14: Rg20 Point (Conventus Omnium Yang).	72
Figure 15: Energy circulation model in the body.	73
Figure 16: Representative scheme of the White ball.	73

Tables Index

Table 1: AJCC-cTNM Clinical Classification System (version 2.2016).	21
Table 2: pTNM Pathological Classification System (version 2.2016).	22
Table 3: Most common side effect of chemotherapy in the management of CRC.	29
Table 4: Summary of research on cancer disease and Qigōng therapy.	63
Table 5: Experiment flow-chart.	69

"God wants, men dream, the work is born."

Fernando Pessoa

"Non-action is the real action. One hundred acts are not as good as one moment of silence. One hundred exercises are not as good as one moment of standing still.

Big action is not as good as small action. Small action is not as good as non-action."



Wáng Xiāngzhāi (王芗齋/王薌齋)

Introduction

The choice of this study's theme was that cancer is a public health problem that requires a physical, social, economic and psychological treatment.

Colorectal cancer is the third most common cancer and the second cause of death in the West. Approximately 5% of colorectal cancers are directly related to heredity or chronic inflammatory disease such as ulcerative colitis; although a family history shows us a prevalence of 25% of this disease. The most colorectal cancers in the Western world are sporadic and could be caused by environmental factors (Holt, Kozuch, & Mewar, 2009).

The present document is a thesis proposal within the framework of the Master degree of Traditional Chinese Medicine, lectured in the Institute of Biomedical Science of Abel Salazar – Oporto University, under the supervision of Prof. Henry Johannes Greten and Prof. António Araújo and co-supervision of *Qigōng* Specialist Mário Gonçalves.

Qigōng is a system of exercises present in Chinese population for thousands of years and have been used to improve their mental and physical Health (Duarte, 2013).

However, *Qigōng* practice has some particular features. It is generally a more dynamic approach than the other meditative traditions and its movements are said to stimulate acupuncture meridians.

The neuroendocrine and immune system seems to have some psychosomatic interactions. The neuroendocrine system influences immune function through hormonal and neural pathways, while the immune system affects neuroendocrine function through the cytokines.

Qigōng appears to be linked with the psychological state of the individual because it stimulates some cerebral areas associated with neuroendocrine system, whereby influence on immune cells production (Manzaneque, Juan M, Francisca, 2004).

The main purpose of this study is to evaluate the effect of *Qigōng* in immunity system, specifically in NK cells, on patients with colon-rectal cancer. Simultaneously, it intends to demonstrate the feasibility of integrating these exercises in cancer treatment a pair of conventional medical treatments.

We also attempt to assess if and how the effects related with *Qigōng* can be related with anxiety and depression in daily life of this patients and if they have a reduction of side effects caused by cancer treat..

Chapter I – Literature Review

To be able to understand the state of Cancer and their complex interrelationship with the immune system and the role of *Qigōng* to improve this state we performed a comprehensive literature review. The criteria used for inclusion of articles for this literature review were: databases, Google Scholar, PubMed, Science Direct and others.

To achieve this goal we used the keywords: Immunology, Colorectal Cancer, Psychoneuroimmunology, *Qigōng* and Traditional Chinese Medicine.

The literature review is divided into 5 key posts. First refers to the epidemiology of CRC and its definition. Second point related to immunity and its role in cancer and their relationship with psychological and neurological factors. Finally the correlation between these concepts and Traditional Chinese Medicine (TCM) according to the model of Heidelberg and the benefits of *Qigōng* in the cancer treatment.

1. Colorectal Cancer Overview

1.1.Epidemiology and Etiopathophysiology

Colorectal cancer (CRC) is the 3rd most common form of cancer worldwide, with approximately one million new cases diagnosed per year. Report data GLOBOCAN 2008 International Agency for Research on Cancer (IARC) shows that colorectal cancer is the third most common form of cancer in men (663,000 cases, 10% of the total) and the second most common in women (570,000 cases 9.4 % of the total) in the world (Ferlay et al., 2010).

It affects about 148,300 individuals which 56,600 of them deaths annually in the United States (Adams, Thorpe, Becker, Joski, & Flome, 2004).

According to the World Health Organization (WHO), the CRC is the most common cancer in the European Union. About 4% of European men and 3% of European women will develop CRC up to 75 years (Melo & Braga, 2003).

The CRC is a worldwide health problem with an annual incidence of approximately 1,000,000 of cases and a higher mortality to 500,000 cases per year (Cotter et al., n.d.).

In Portugal, the incidence of CRC is almost similar in both sexes, though colon cancer is slightly more common in women and rectal cancer in men. According to the Northern Regional Cancer Registry (RORENO) from 5171 malignant tumors diagnosed in 2006, 311 (6%) of them were colon and 387 (7.5%) of them were rectum (PONTES, L., 2010).

Regarding to the mortality, the country with the highest mortality rate is Hungary and Greece has the lowest for both sexes. Portugal is in the 7th place for males and the sixth for females.

In Portugal mortality from CRC has increased significantly in recent decades, with an annual average rate of 4%. In 1999 the CCR has been responsible for 2828 deaths and considered the leading cause of death from cancer that year. According to statistics, in 2005 the rate of mortality with CRC was 14.6%, corresponding to 3319 deaths per year and more than nine deaths per day. Currently the CRC is the first cause of death from malignancy in Portugal (Esteves Alves do Forno, Castro Poças, & Gomes Domingues dos Santos Matos, 2012).

In fact, in most countries there was a rate decrease with the exception of Korea, Portugal, Slovenia, Poland, Mexico, Greece, Chile and Estonia.

The most are sporadic appearance, though it may be hereditary/family such as familial adenomatous polyposis (FAP) or hereditary non-polyposis colon cancer (HNPCC), in about 15% of cases.

This disease is uncommon in people under 50 years old (mean age diagnose is 70 years old), however globally the incidence is increasing in young people and to decline in elderly. It affects both sexes similarly, although the rectal cancer is more common in men (Holt et al., 2009).

The human colon is a muscular, tube-shaped organ making part of the large intestine and is divided into four segments: ascending - colon length 15-20 cm long; transverse - colon length 30-60 cm long, descending - colon length 20-25 cm long and sigmoid - colon length 30-40 cm long. It extends from the end of small bowel to anus, twisting and turning through

abdomen. The colon has 3 main functions: digest and absorb nutrients from food, concentrated fecal material by absorbing fluids and store and control evacuation of fecal material.

The destabilization of the genome is a prerequisite for tumor formation. Adenomas and carcinomas arising in the context of genomic instability, when epithelial cells acquire the number of mutations needed to achieve the stage of neoplastic. Polyps may be classified as non -neoplastic or neoplastic.

The non-neoplastic may arise in due to abnormal maturation of mucosal inflammation or anomalies of architecture, without malignant potential. In this type of polyps include hyperplastic the hamartomatous, inflammatory and lymphoid cells. Hyperplastic represent about 90% of epithelial polyps of the large bowel. These result from the reduced renewal of epithelial cells with mature cell accumulation on the surface (Pais, 2013).

The polyps which arise as a result of proliferative epithelial dysplasia, adenomatous or adenomas constitute a precursor of neoplastic carcinoma lesions.

The degree of adenoma dysplasia can vary between low and high grade. The high-grade dysplasia is between adenoma and adenocarcinoma.

About 95% of the colorectal cancers are epithelial-derived adenocarcinomas; their initial presentation is a benign adenoma that by mutation in key genes such as adenomatous polyposis coli (APC), K-ras and TP53.[48] 3-6 Aberrant crypt foci (ACF), small areas of epithelium that display irregular glandular architecture, gives rise to adenomas (Takhar, Eremin, & Watson, 2004).

The mutations are either hereditary and/ or environmental factors. These result from chromosomal instability, such as losses in portions of chromosome 5q, 18q and 17p (containing tumor suppressor genes), mutations of oncogenes and microsatellite instability. The major tumor suppressor genes affected are APC (5q), DCC/MADH2/ MADH4 (18q) and TP53 (17p) and exist alongside activation of key oncogenes, such as K-ras.12-14. The loss of the APC gene appears to be one of the earliest events in colorectal tumor progression and can be either somatic or germline, the latter leading to familial adenomatous polyposis (FAP) (Esteves Alves do Forno et al., 2012).

There are two routes to the pathogenic development of the CRC, the route APC/ β - catenin and the microsatellite instability (MSI).

The mutations in the APC gene can be inherited from the parents, such as familial adenomatous polyposis (FAP) and Hereditary no-polyposis colon cancer (HNPCC) or can be acquired after birth through somatic mutations.

Approximately 80% of adenomatous polyps are the APC gene mutations. This protein plays a key role and its dysfunction leads to chromosomal instability. The morphological evolution of these dysfunctions is: epithelial proliferation in the colon, small adenoma formation, gradual increase of adenomas and its grade of dysplasia and finally cancer appearance. This is called "adenocarcinoma sequence" (Moreira, n.d.).

Molecular model for the evolution of colorectal cancers through the adenoma-carcinoma sequence

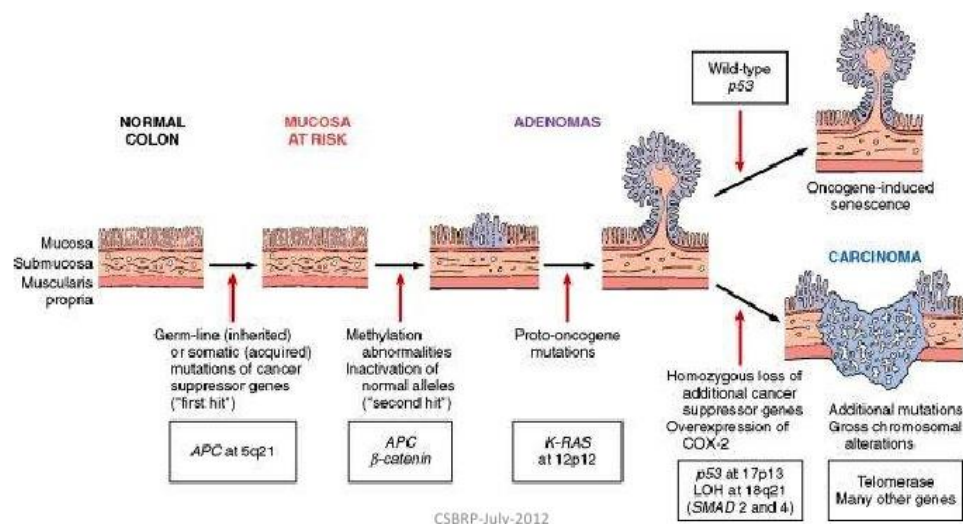


Figure 1: Molecular model of adenocarcinoma sequence.

Source: <http://3.bp.blogspot.com/-7AUweN9wps0/T5nBNLqDGhI/AAAAAAAAAGo/QnMsOrW-v9A/s759/carcinogenesis.jpg><http://patologiab.blogspot.pt/>

About 15% of CRC are formed through the alternative pathway MSI. This pathway occurs through pathogenic mutations in target genes that are acquired and lead to aberrant growth and possible malignant transformation. Acquired mutations are persistent when

malignant lesions are a result of DNA repair defects, through microsatellite instability, for example in mismatch repair genes. These cancers typically show. Usually DNA microsatellites presents high myotonic instability in these malignant cells (the repeating units of DNA that occur normally throughout the genome). This genetic pathway that leads to the appearance of HNPCC and FAP enhances progression in CRC (Esteves Alves do Forno et al., 2012).

1.2.CRC Clinical Presentation and Staging

The staging is an importance key because it is a strong predictive factor of survival.

Depending on the extent of the cancer throw the body, they can be classified in stages. When we talk about colorectal cancer, the stage is defined by the how far the cancer has grown into the intestine wall, the extent to the nearby structures, the lymph nodes and other distant organs. The choice of the best treatment and the prognosis are defined by the stage of the malignant lesions. Every time that staging is based on the physical exam, biopsy and imagiological tests we are defining a clinical stage of the disease. If the stratification is made with the association of the surgery findings and the clinical statement, the pathological stage is defined. Pathologic stage is used to describe the extent of the cancer (Catarina & Ribeiro, 2010).

The most commonly used staging system for colorectal cancer is the American Joint Committee on Cancer (AJCC), sometimes also known as the TNM system (Ajcc, 2009). The TNM system describes the 3 most important findings in the tumor staging: T (evaluation of how far the primary tumor has grown through the intestine wall and the nearby regions); N (stratification of the extent of spread to regional nearby lymph nodes); M (localization of the cancer metastasis to the other organs). Colorectal cancer metastasis can be found anywhere, especially in liver and lungs ("How is colorectal cancer staged?," 2015).

TNM Classification – Definitions for T, N, M					
Primary Tumor (T)		Regional Lymph Nodes (N)		Distant Metastasis (M)	
T _x	Primary tumor cannot be assessed	N _x	Regional lymph nodes cannot be assessed	M ₀	No distant metastasis
T ₀	No evidence of primary tumor	N ₀	No regional lymph node metastasis	M ₁	Distant metastasis
T _{is}	Carcinoma in situ: intraepithelial or invasion of lamina propria	N ₁	Metastasis in 1–3 regional lymph nodes	M _{1a}	Metastasis confined to one organ or site
T ₁	Tumor invades submucosa	N _{1a}	Metastasis in one regional lymph node	M _{1b}	Metastases in more than one organ/site or the peritoneum
T ₂	Tumor invades muscularis propria	N _{1b}	Metastasis in 2–3 regional lymph nodes		
T ₃	Tumor invades through the muscularis propria into pericorectal tissues	N _{1c}	Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis		
T _{4a}	Tumor penetrates to the surface of the visceral peritoneum	N ₂	Metastasis in 4 or more regional lymph nodes		
T _{4b}	Tumor directly invades or is adherent to other organs or structures	N _{2a}	Metastasis in 4–6 regional lymph nodes		
		N _{2b}	Metastasis in 7 or more regional lymph nodes		

Table 1: AJCC-cTNM Clinical Classification System (version 2.2016).

Source: www.nccn.org/patients

In the attempt to perform the best cancer staging, all the elements are combined to acquire a score (roman numbers classification): the higher is the number, most advanced is the disease. This is generally how the cancer is referred to between doctor and patient.

Anatomic Stage/ Prognostic groups			
Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
	T2	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-T2	N1/N1c	M0
	T1	N2a	M0
IIIB	T3-T4a	N1/N1c	M0
	T2-T3	N2a	M0
	T1-T2	N2b	M0
IIIC	T4a	N2a	M0
	T3-T4a	N2b	M0
	T4b	N1-N2	M0
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b

Table 2: pTNM Pathological Classification System (version 2.2016).

Source: www.nccn.org/patients

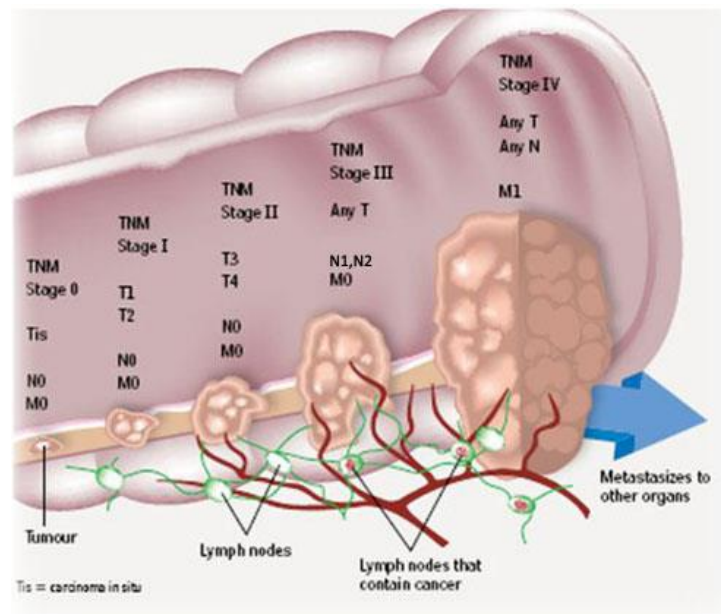


Figure 2: TNM Classification System.

Source: http://3.bp.blogspot.com/_U4l5ZnkjE/TTxe1Osa1/AAAAAAAAADM/J-wOG86HmIE/s320/Capture-5.jpghttp://cancerology.blogspot.pt/2011_01_23_archive.html

As well as the stage of bowel cancer, the grade refers what the cancer cells look like under the microscope and helps to decide the treatment because it is an indicator of prognosis. The grade tells how normal or abnormal the cancer cells are. A pathologist grades bowel cancer as: Grade 1 (low grade) – the cancer cells are well differentiated, which means they look quite similar to normal cells; Grade 2 (moderate grade) – the cancer cells are moderately differentiated, which means the cells look more abnormal; Grade 3 (high grade) – the cancer cells are poorly differentiated, which means they look very abnormal (“Staging and Grading,” n.d.).

The grade gives idea of how the cancer is likely to behave. A low grade cancer is likely to be slower growing and less likely to spread than high grade cancers.

1.3.Risk factors

Researchers have found several risk factors that may increase a person's chance of developing colorectal polyps or colorectal cancer.

The risk of getting colorectal cancer increases with the older age. More than 90% of cases occur in people who are 50 years old or older.

Certain types of diet promote the appearance of CRC. According to Friedman and colleagues, the first nutrients to be identified as risk factors for promoting adenoma were fats and simple sugars ingested in excess. In fact, high intake of simple sugars is responsible for glycemic overhead associated with the risk of CRC. Several studies indicate that fats may alter not only the concentration of normal bodily products (cholesterol and bile acids), as well as the normal flora of the intestines. This process appears to act as a cancer promoter, damaging the mucosa of the colon and increasing the proliferative activity of the colonic epithelium. Some articles show that diets containing large proportions of fat predisposes to the CRC, especially the descending and sigmoid colon (Esteves Alves do Forno et al., 2012).

There are other dietary factors that act as promoters of the carcinogenic process and which include the genotoxic carcinogens such as grilled meat on charcoal , fish and fried foods. A diet rich in red meat (such as beef, pork, lamb or liver) and processed meat (food like hot

dogs or luncheon meats) can increase the risk for colorectal cancer ("Colorectal cancer risk factors," 2015).

There are also factors leading to a decrease of CRC risk and which have a protective effect against the same. The increasing intake of fiber not only can protect the CRC appearance, but also bring other health benefits in general (Dahm et al., 2010).

Another one is the protective role of milks fermented with probiotic cultures in colon cancer risk reduction. Many studies showed that probiotics may beneficially modulate several major intestinal functions: detoxification, colonic fermentation, transit, and immune status, which may accompany the development of colon cancer (Saikali, Picard, Freitas, & Holt, 2004).

The sedentary lifestyle can contribute to increase the risk of this cancer. Studies show that individuals of both sexes in sedentary occupations have an increased risk of colon cancer and that the risk decreases progressively for jobs that require a high level of physical activity. Physical inactivity has been associated with the risk of CRC further into the colon cancer than for rectal cancer.

Overweigh and obesity raises the risk of colon cancer in both men and women, but the link seems to be stronger in men. Visceral adiposity is associated with low-grade chronic inflammation leading to up-regulation of the nuclear transcription factor- κ B (NFK β) with transcription of genes that promote tumorigenesis as a consequence.

Long-term smokers are more likely than non-smokers to develop and die from colorectal cancer and alcohol users tend to have low levels of folic acid in the body which is also a predisposition to the onset of disease (Esteves Alves do Forno et al., 2012).

Studies have shown that subjects having adenomatous polyps of the colon have greater risk of developing new polyps which, according to the adenoma - carcinoma sequence - may evolve to CRC. Also inflammatory bowel disease (IBD), which includes ulcerative colitis and Crohn's disease, is a condition in which the colon is inflamed over a long period of time. People who have had IBD for many years often develop dysplasia and these cells can change into cancer over time.

There is evidence that hereditary factors also contribute to the onset of CRC. Genetic factors play an important role in the initiation, development and progression of adenomatous polyps. Heredity associated with the large bowel cancer can be divided into two main groups: polyposis syndromes and non- polypoid syndromes.

Colorectal cancer is associated with cancer family syndromes; about 5 to 10% of people with colorectal cancer history have inherited gene defect. These syndromes often lead to cancer that occurs at a younger age. The most common inherited syndromes linked with colorectal cancers are familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC) (Catarina & Ribeiro, 2010; Esteves Alves do Forno et al., 2012; Moreira, n.d.).

1.4.Diagnose of CRC

Colorectal cancer is a symptomatic disease, but not every time. Many times those with early colon or rectal cancer do not have symptoms: they usually appear in more advances stages of the disease. It is very important the physical exam and the analysis of blood tumor markets and liver enzymes. The occult blood stool test can also detect small intestinal bleeding that may occur intermittently and invisibly in some CRC and medium-sized polyps.

The symptomatic presentation can be divided in two groups: symptoms that derive from the local tumor and symptoms related to metastasis.

The major symptoms associated with colorectal cancer are: melena or haematochezia, abdominal pain, unexplained iron deficiency anemia and a change in bowel habits. Abdominal distension, nausea and vomiting are less common and suggest obstruction, as an indicator of the presence of a cancer that encircles the bowel. Rectal cancer can also cause tenesmus, rectal pain and diminished calibre of stools.

The most common symptoms suggesting metastatic disease are right upper quadrant pain, abdominal distension, early satiety, supraclavicular adenopathy and periumbilical nodules; all those major symptoms are related to regional lymph nodes, liver, lungs and peritoneum (Esteves Alves do Forno et al., 2012; Pais, 2013).

In the suspicion of colorectal cancer, based on clinical history, physical exam or tests results (specially blood tests) other tests are recommended: abdominal ecographic tests, x-rays, magnetic fields and radioisotope imaging techniques, all based on the better definition of the bowel.

Sigmoidoscopy is an endoscopic examination using a sigmoidoscope. A flexible lighted tube with a lens to view and a tool to remove tissue are introduced in the rectum and sigmoid colon. This instrument is inserted through the anus into the rectum and sigmoid colon as air (or carbon dioxide) is pumped into the colon to expand. During sigmoidoscopy, abnormal growths in the rectum and sigmoid colon can be removed for analysis (biopsy).

The most often is colonoscopy. They are also an endoscopic examination that allows the complete observation of the colon from the rectum to the blind. It has the advantage of allowing the removal of malignant or pre-malignant lesions by polypectomy combining screening and treatment in one safe examination. This test identifies over 25% of early lesions not detected by other methods and it is the gold standard test in screening of target lesions because this higher sensitivity.

Normally imaging tests are done to help find out the cancerous` areas, to learn how far cancer may have spread, and to help determine if treatment has been effective (Esteves Alves do Forno et al., 2012; "How is colorectal cancer diagnosed?," 2015).

1.5.Treatment of CRC

The therapeutic modalities available for the treatment of CRC include surgery, chemotherapy and radiotherapy as well as new anti-angiogenic drugs, therapeutic targets of cancer. They are also in great development the immune directed therapeutics. Different therapeutic options are different according to the tumor stage - size, location and metastasis, as well as the physical condition of the patient (George, 2013).

The goal of surgery is a wide resection of the involved segment of the bowel together with removal of its lymphatic drainage, and the resection should include a segment of colon of at least 5 cm on either side of the tumor, although wider margins are often included due to obligatory ligation of the arterial blood supply.

Chemotherapy aims to increase overall survival, increase the disease-free interval and increase the quality of life.

When used as a palliative treatment for pain decrease, we can see this as one option to increase the quality of life of patients in the end-stage of the disease.

It may be administered in two ways: systemic chemotherapy (intravenous or oral administration) and regional chemotherapy (administration into the artery to particular body area that contains the tumor) (Fernandes Jr. et al., 2011).

Chemotherapy may also be used at different times: **Adjuvant chemotherapy** is used after the surgery for tumor resection. It helps to prevent a new cancer formation and it is proved to prolong the lifetime of patients with colorectal cancer in the stages II and III. Adjuvant chemotherapy works by reducing the cancer cells that can even be presents after surgery and those ones that can be located in other parts of the body.

Neoadjuvant chemotherapy is given before surgery to try to shrink the cancer and make surgery easier.

Palliative chemotherapy is used for shrink tumors and relieve metastatic symptoms in most advanced diseases. It's not a cure, it's a way to increase lifetime with the best life quality possible. (Barrett & Le Blanc, 2009; Catarina & Ribeiro, 2010; Pais, 2013).

Patients with CRC, stages 0 and I has a probability of 90% of cure with surgery. There are no studies showing benefit in the use of adjuvant chemotherapy, and the only treatment is surgical.

The CRC stage II comprises T3 or T4 tumors without lymph node and distant metastasis. It is a group of good prognosis, with 5-year survival around 80%. The recommended treatment for these patients consists in surgery, with or without adjuvant chemotherapy.

Patients in stage III, after surgical treatment, have benefit with adjuvant chemotherapy.

Most patients with metastatic colon cancer in the stage IV cannot be cured, and palliative chemotherapy is the only treatment. The survival of a patient who does not receive palliative chemotherapy is approximately five to six months (Fernandes Jr. et al., 2011).

The chemotherapy more used in the CRC is very strong and can also affect some healthy cells in the body. It is given in cycles, with each period of treatment followed by a rest period to allow the body time to recover. Chemotherapy cycles generally last about 2 to 4 weeks.

The drugs most often used for colorectal cancer include: 5-Fluorouracil (5-FU), synthetize inhibitor thymidylate, which is often given with leucovorin (also called folinic acid) that increases the affinity of this agent for the target. There is evidence that compared to the 5-FU isolated administration, 5-FU and LV association increases the rate of therapeutic response with improved of the survival. Among patients with metastatic CRC, about 20%, register a reduction of 50% in tumor size, with increased survival from 6 to 12 months. 5-FU is commonly administered intravenously infusion and better tolerated than bolus with a lower incidence of side effects like diarrhoea and neutropenia. It may also be given by oral form with name, Capecitabine with similar efficacy to 5-FU intravenous. (Catarina & Ribeiro, 2010).

Currently, the recommendations indicate the use of a drug combination as first-line chemotherapy, there is already evidence that the combination of 5-FU, LV and oxiplatina have greater therapeutic benefit than the isolated administration of 5-FU and LV. The Folfox scheme is the combination of oxiplatina, 5-FU bolus and continuous infusion and LV is the standard therapy in stage III and with good results in stage IV. The Folfori scheme combines irinotecan, the LV and 5-FU. Recent studies have shown that therapeutic Folfori increases toxicity without significant improvement of the survival results in the adjuvant chemotherapy (Catarina & Ribeiro, 2010; Fernandes Jr. et al., 2011; Pais, 2013).

In advanced CR treatments may be combined with chemotherapy agents that inhibit cell proliferation or angiogenesis. Cetuximab and bevacizumab are humanized monoclonal antibodies that recognize and specifically bind to other proteins in the body.

This prevents tumor growth by blocking the growth of blood vessels that supply oxygen and nutrients to the tumor.

The choice of the most adequate drugs for chemotherapy and the length of the treatment define the majority of the side effects: hair loss, mouth sores, loss of appetite, nausea, vomiting and haematological disorders. (Pais, 2013).

Regimens	XELOX (capecitabina + oxaliplatin)	FOLFOX (5-FU/LV/oxaliplatin)	FOLFIRI (5-FU/LV/irinotecan)
Side effects	<input type="checkbox"/> Nausea and vomiting	<input type="checkbox"/> Risk of infection	<input type="checkbox"/> Nausea and vomiting
	<input type="checkbox"/> Diarrhoea	<input type="checkbox"/> Diarrhoea	<input type="checkbox"/> Risk of infection
	<input type="checkbox"/> Hand-Foot syndrome	<input type="checkbox"/> Mouth sores	<input type="checkbox"/> Mouth sores
	<input type="checkbox"/> Neuropathy	<input type="checkbox"/> Han-foot syndrome	<input type="checkbox"/> Anemia
		<input type="checkbox"/> Numbness or tingling	
		<input type="checkbox"/> Plantar-palmar syndrome	
Type	Neoadjuvant treatment	Adjuvant treatment	Palliative treatment

Table 3: Most common side effect of chemotherapy in the management of CRC.

Source: <http://fightcolorectalcancer.org/fight-it/managing-side-effects/http://beasurvivor-colorectal.com/side-effects-of-chemotherapy/>

Chemotherapies induces immunosuppression, local or systemic, and may affect the formation, recruitment and the action of the immune system cells and thereby precipitate a treatment failure. According to some studies, tumors that have lymphocyte infiltration (TIL) are those who respond best to chemotherapy.

The main targets for chemotherapeutic agents are the tumor itself and the various subtypes of lymphocytes, antigen presenting cells. Most of these agents cause DNA damage by affecting the proliferation, maturation and function of various cells - particularly lymphocytic cells , antigen presenting cells , dendritic cells and Natural Killer cells (NK) It conditions the function, modulation and recovering of the immune system (Barrett & Le Blanc, 2009; Florea & Büsselberg, 2011; Nüssler et al., 2007).

2. Immunology

2.1. Immunologic System

The infectious disease has declined in the Western world and cancer has become the second leading cause of death, topped only by heart disease (Parham Peter, 2011).

From an immunologic perspective, cancers cells can be viewed such as altered self-cells that have escaped from normal growth-regulating mechanisms. The various types of mature cells in the body have a given life span. When these cells die, new cells are generated by the proliferation and differentiation of various types of stem cells. This cell growth and proliferation are essential for wound healing and homeostasis. Occasionally cells arise no longer respond to normal growth control mechanisms and proliferate in an unregulated manner producing a tumor or neoplasm (U.S. Department of health and human services, 2003).

The immune system is a network of cells, tissues, and organs that work together to protect the body against attacks by “foreign” invaders. It is constituted by several cell types each with different functions and distributions in the body.

This mechanism can be divided into innate and adaptive immunity. The innate immunity is the first organic defense that is continually ready to respond to invasion. It is constituted by epithelial skin, gastrointestinal tract, respiratory tract, granulocytes, monocytes, natural killer cells, dendritic cells and circulating plasma proteins. The adaptive immunity is constituted by lymphocytes and it is a very complex body answer because it recognizes and remembers self-cells distinguish from foreign cells and destroy them. This is because some of the activated T and B cells become memory cells. The foreign cells are called an antigen and can be a microbe, a virus, a part of a microbe or a transplanted cell (Owen, Judith A., Punt, Jenni, Stranford, 2013; Parham Peter, 2011; U.S. Department of health and human services, 2003).

All cells of the immune system have their origin in the bone marrow. The most important components in the immunity system are lymphocytes and the natural killer cells.

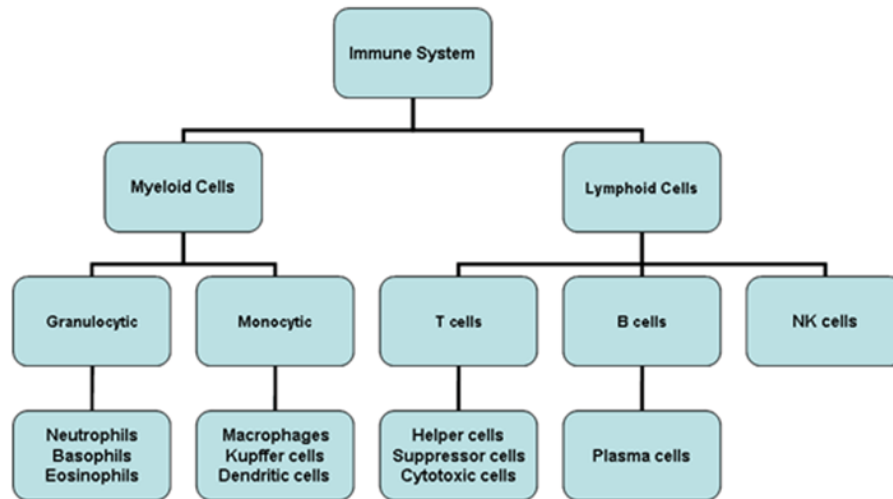


Figure 3: Immune system types of cells.

Source:(Owen, Judith A., Punt, Jenni, Stranford, 2013).

The lymphocytes (B lymphocyte, T lymphocyte) have origin in lymphoid progenitor (stem). The T cell not recognize free-floating antigens because their surface doesn't contain specialized antibody receptors. For T cells development the precursor T cells must migrate to the thymus where they undergo differentiation into two distinct types of T cells, the CD4+ T helper cell and the CD8+ pre-cytotoxic T cell. Two types of T helper cells are produced in the thymus the Th1 cells, which help the CD8+ pre-cytotoxic cells to differentiate into cytotoxic T cells, and Th2 cells, which help B cells, differentiate into plasma cells, which secrete antibodies (Parham Peter, 2011).

The B lymphocyte has a surface receptor specific for each antigen and they are responsible for the production of antibodies.

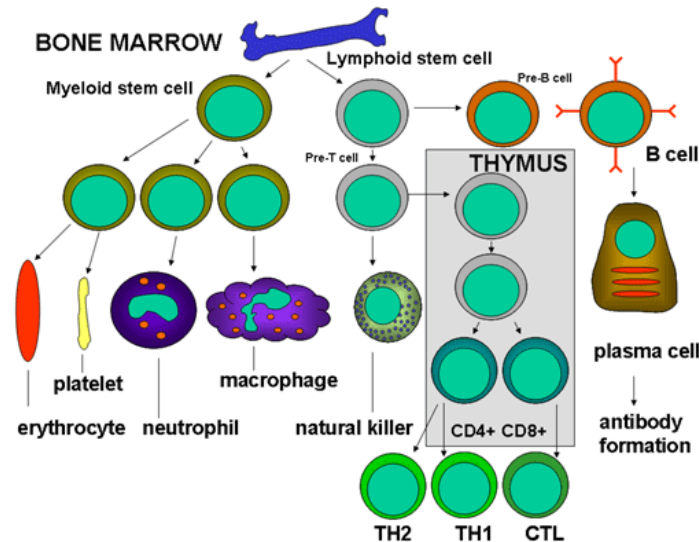


Figure 4: The division of the Lymphoid stem cell.

Source: <http://www.microbiologybook.org/ghaffar/devel-immune.gif>
<http://www.microbiologybook.org/French-immuno/immchapter1.htm>

The cells that are in the line of defence in the non-specific immune system are polymorph nuclear eosinophils and macrophages. The Neutrophils are Polymorph nuclear cells (PMNs) that act on the in phagocytosis process to kill in intracellular process. In addition, PMNs contribute to collateral tissue damage that occurs during inflammation.

Natural killer (NK) and lymphokine activated killer (LAK) cells can non-specifically kill virus infected and tumor cells. These cells are not part of the inflammatory response but they are important in nonspecific immunity to viral infections and tumor surveillance.

There is another important component in the immune system called cytokines. Cytokines are a large group of proteins, peptides or glycoproteins that are secreted by specific cells of immune system. Cytokines are a category of signalling molecules that mediate and regulate immunity, inflammation and haematopoiesis. They include a diverse assortment of interleukins (IL), interferons (IFN) and Tumor Factor Necrosis (TFN), chemokine (CC), Growth Tumor Factor (GTF) and Colony Stimulanting Factor (CSF) (Faria, 2014).

The inflammatory cytokines such as IL-1, IL6 and TNF- α act on the control center of the temperature, the hypothalamus elevating the temperature sensation of the body. This measure helps the immune system to fight infection because viral and bacterial agents replicate faster at

low temperatures. Humoral immunity is mediated by cytokines such as IL-4, IL-5, IL-6, IL-10 e IL-13.

Other cytokine also being study for their potential development of immunologic disease is IL-2. Clinical studies are testing its benefits in the cancer, hepatitis and HIV infection and AIDS. Studies say that CSF stimulates the production of neutrophils in cancer diseases in patients who have been submitted to chemotherapy (Owen, Judith A., Punt, Jenni, Stranford, 2013; Pais, 2013; Parham Peter, 2011).

The immunity can be strong or weak, short-lived or long-lasting depending on the type of antigen, the amount of antigen, and the route by which it enters the body. It can also be influenced by inherited genes and immunization with vaccines can provoke an immune response but not full-blown disease (U.S.Department of health and human services, 2003).

2.2.NK Cells

The natural killer cells natural killer (NK) cells were among the first cell type to be recognized for their inherent ability to destroy tumor cells, from which their name derives. They are large and granular lymphocytes that works in innate immunity specially defence against viral infections. This phenotype is characterized by surface markers CD3- and CD56+ and they can be localized into spleen, liver, lymph nodes, bone marrow, peritoneal cavity and placenta. Account for about 10-15% of circulating lymphocytes in blood they are a similar function with cytotoxic T cells both kill infected cells and can produce cytokines. Any NK cells and T lymphocytes has many similar surface molecules involved in the elimination of virus infected cells and tumors cells (Parham Peter, 2011)

The T lymphocytes (CD8 +), belonging to adaptive immunity, requiring prior sensitization to activate while NK cells don't need a specific antigen to be activated (Faria, 2014).

These cells were found exclusively in innate immunity due to the low specificity of antigen- antibody surface receptors. Nowadays studies show that they have immunological memory and they can recognise the same infectious agent after to be exposing to them making part of the adaptive immunity too.

NK cells have recognition mechanisms and use a series of surface receptors that respond to a balance of activating and inhibiting signals delivered by self-cells. They have the ability to lyse virus-infected cells that do not express the molecules of the major histocompatibility complex (MHC) inducing cell death by apoptosis. The MHC cells are divided into two classes: I class and II class. The activity of de NK is induced by stress cell and it is inhibited by the MHC proteins class I. Many virus-infected or tumor cells lose expression of their MHC proteins and they don't send these inhibitory signals. Receiving an excess of activating signals compared to inhibitory signals indicate that a target cell is abnormal, and the NK cell is activated to kill the target cell (Owen, Judith A., Punt, Jenni, Stranford, 2013; Parham Peter, 2011).

The normal body cells are not exposed to destruction by NK cells because all nucleated cells express MHC class I molecules that become tolerant to the immune system.

The cytokine production mediated by NK cells has an impact on the production of dendritic cells , macrophages and neutrophils as well as having a regulatory function (Faria, 2014).

2.3.Cancer and natural killer cells

Tumor growth is a complex process that depends on several interactions between the tumor and surrounding tissues. It depends on the immune system function and the capacity to infiltrating lymphocytes in the tumor location and their correlation with survival of cancer patients.(Owen, Judith A., Punt, Jenni, Stranford, 2013).

Studies show that NK cells can control both local tumor growth and metastasis due to their ability to exert direct cellular cytotoxicity without prior sensitization and to secrete immunostimulatory cytokines like IFN- γ . They are also a part of the system for cancer elimination: inhibiting cellular proliferation and angiogenesis, they promote apoptosis and the adaptaion of the immune system, essential for Ag processing and presentation. (Levy, Roberti, & Mordoh, 2011).

Waldhauer (2008) studied the contribution of NK cells to the immunosurveillance of tumors and the molecular mechanisms that allow NK cells to distinguish malignant from healthy cells. Particular emphasis is placed on the activating NK receptor NKG2D, which recognizes a variety of MHC class I-related molecules believed to act as 'immuno-alerters' on malignant cells (Waldhauer & Steinle, 2008).

According to the immunoediting theory cancer cells and immune cells reciprocally modulate each other and the two possible outcomes are: the elimination or the escape of tumor cells. NK cells are considered to represent a first line of defence against the metastatic spread of tumor cells (Pais, 2013).

The role that the immune system plays in cancer therapy is controversial. The immunotherapy is how to prevent or treat diseases through the increased induction or suppression of the immune response against a particular pathogen or neoplastic cell. There are two types of immunotherapy: active immunotherapy (vaccination) and passive immunotherapy (use of immunoglobulin and antibodies, allergens immunotherapy and cancer immunotherapy). The use of NK cell in the immunotherapy has been studied. One way to do that is to use NK cells from healthy donors isolate and activate them in vitro before being placed in the patient with cancer. Another way is to obtain stem cells and progenitor cells coming from umbilical cord blood or from placenta (cryopreservation). The most important is the future perspective that immunotherapy using NK cells associated with others types of treatments such as chemotherapy, radiotherapy and biologics therapies can promote an increased anticancer action (Alici & Sutlu, 2009; Cheng, Chen, Xiao, Sun, & Tian, 2013; Levy et al., 2011).

2.4.CRC and Immunologic System

The best defence against cancer is not only in the cells of the immune system but also in the global cells the human body. The integrity of the body depends on many factors such as a controlled cell division, a capacity of DNA damage repair and an uncontrolled division and replication this. So for cancer appearance there must be multiple genetic mutations occurring in genes related to the control cell proliferation and cell survival. Despite the heterogeneity of different cancer diseases, all cancers have common characteristics: they stimulate their own growth, prevent the apoptosis death, connected to the circulatory system, expand its population

and leave their origin place to invade new tissues and to be successful must be able to trick the immune system (Pais, 2013; Parham Peter, 2011).

A healthy immune system is necessary for control malignant cells proliferation associated with cancer progression.

A study show that the cancer incidence increases among transplant patients using immunosuppressive drugs.

Another study shows that people with immunodeficiency are more susceptible to developing cancer. So, people with cancer survival correlates directly with an efficient adaptive immune response. The immune system has a function called immunosurveillance that allows recognizing cancer cells and eliminating them before they cause disease (Pais, 2013).

2.5.Psychoneuroimmunology and Cancer

Psychoneuroimmunology also termed neuroimmunomodulation is the medical science which studies the psychochemical mediation and the influence of emotions and consciousness states on the immune system (Lissoni et al., 2008).

The basis of this model says that psychosocial stress decreases the efficiency of the immune system which leads to an increase in disease symptoms. Psychosocial factors affecting the immune system are the emotional state, the type and intensity of stress, the characteristics of the personality and the quality of relationships (Alves & Palermo-Neto, 2007; Daniel-ribeiro & Martins, 2009; Lissoni et al., 2008)

The immune system is mediated by differences in the central nervous system activation, the hormonal response and the behavioural change related to the psychological state of the person. Some investigators found the relationship between the immune system and the endocrine system through the existence of NK cell receptors for specific neurotransmitters or hormonal mediators such as catecholamine, cortisol, prolactin, ACTH, TSH, growth hormone or endogenous opiates. Another connecting factor between these two systems is the existence of sympathetic and parasympathetic nerves of lymphoid organs. Another aspect that affects the

immune system is related to human behaviours associated with reducing of stress such as smoking, diet problems and lack of rest (Alves & Palermo-Neto, 2007; Lissoni et al., 2008).

Some studies done in students during the examination period, show that there is a decrease in the NK cells production and activity compared to the holiday period.

Cohen (1993) studied the relation between depression and immunosuppression collusion that depressed people have a lower production of lymphocytes and a lower activity of NK cells too.

The application of the Psychoneuroimmunology to medical oncology does not relate only to cancer therapy but also to the physio-pathological interpretation of the neoplastic disease and the mechanism of its progression. This theory says that the immunosuppressive status depends not only on the primary damage to immune cells but also on the alterations of the psychoneuroendocrine regulation and on anticancer immune response (Lissoni et al., 2008).

Recent advances show that immune response is physiologically under a psychoneuroendocrine regulatory control and it is mainly stimulated by the pineal gland and inhibited by the opioid system. Paolo Lissoni, 2008 studied the progression of neoplastic disease and the association with progressive deficiency of the neuroendocrine system responsible for the psychochemical stimulatory influence on anticancer immunity in particular of the nocturnal production of the pineal immunomodulation oncostatic hormone melatonin (MLT). MLT is responsible for the stimulating interleukin-2 (IL-2) production by acting on a specific MLT receptor expressed by TH1-lymphocytes. Progressive declines in IL-2 and MLT concentrations represent the main immune and neuroendocrine deficiencies characterizing the dissemination of the neoplastic cells. So this neuroendocrines can be characterized by a natural resistance against cancer development and dissemination (Maia, 2002).

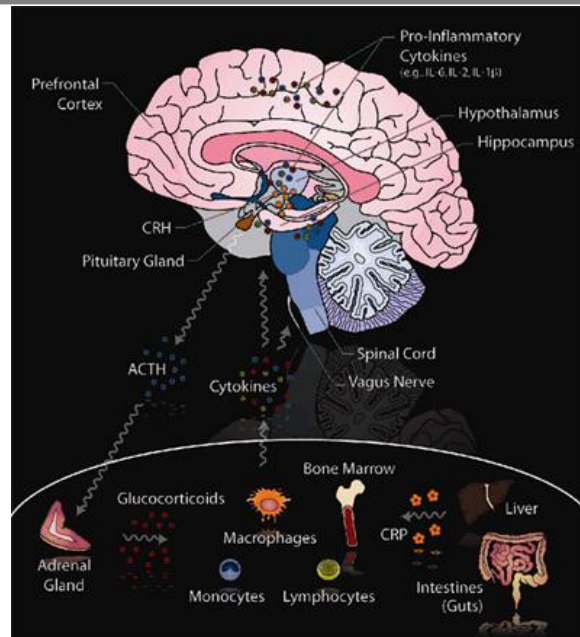


Figure 5: Psychoneuroendocrine regulation system.

Source: http://www.ohsu.edu/xd/education/schools/school-of-medicine/departments/clinical-departments/psychiatry/research/images/lab_1.jpg <http://www.ohsu.edu/xd/education/schools/school-of-medicine/departments/clinical-departments/psychiatry/research/psychoneuroimmunology/>

Some studies with electroacupuncture report that it can modulate the imbalance between the innate and acquired immune systems. Electroacupuncture has been shown to have the ability to adjust the pattern of leukocytes (granulocytes and lymphocytes) in human subjects. Several lines of evidence indicate that this effect is associated with the hypothalamus-pituitary-adrenal (HPA) axis. Notably, hypothalamic messenger RNA (mRNA) expression of proinflammatory cytokines induced by lipopolysaccharide stimulation is reduced by electroacupuncture. It has been reported that lower frequency electroacupuncture (4Hz) produces less of an analgesic effect in animals that have undergone pituitary gland removal (Choi, Lee, & Ernst, 2012).

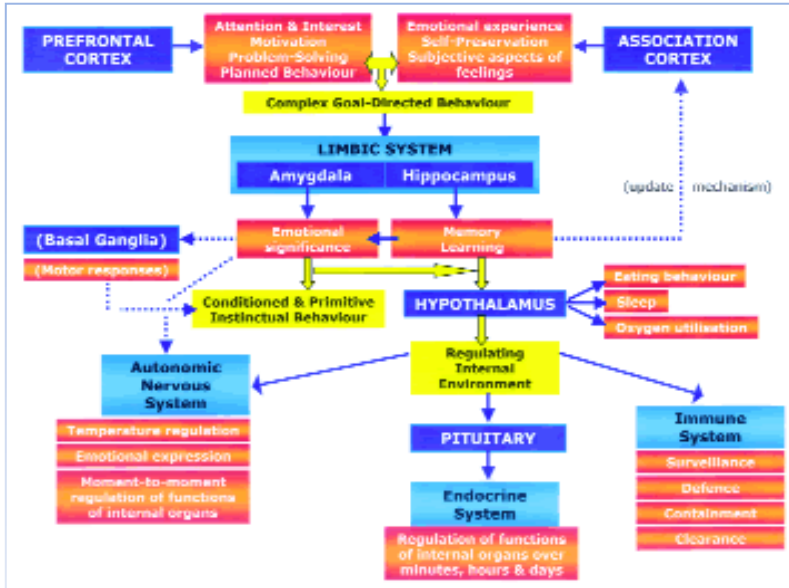


Figure 6: Limbic system explanation.

Source: <http://www.positivehealth.com/img/img/img/imagesoriginal/dbimg/pando88d.gif> <http://www.positivehealth.com/article/pni/cinical-psychoneuroimmunology-mind-body-integrated-health>

Furthermore, psychological and emotional stress has negative implications for increased symptom perception and poor quality of life.

Psychological stress may have multiple negative impacts on health outcomes, namely with a) higher incidence of infections, accelerated aging, and greater cardiovascular diseases in several populations; b) in breast cancer patients, with low physical and psychological QLQ and significantly shorter disease-free interval; and with a decrease of efficacy or resistance to chemotherapeutics agents.

Cancer patients have more susceptibility to have depression and anxiety, which was associated with higher frequency and severity of clinical symptoms, such as pain, fatigue, poor appetite, sleep disturbance and poor quality of life.

Generally, QLQ covers the subjective perceptions of the positive and negative aspects of cancer patients' symptoms, including physical, emotional, social, and cognitive functions and, importantly, disease symptoms and side effects of treatment (Pais, 2013).

Quality of Life is not simply to define it could be: • the state of well-being that is a composite of two components: the ability to perform everyday activities that reflect physical, psychological, and social well-being; and patient satisfaction with levels of functioning and control of the

disease; • is the subjective evaluation of the good and satisfactory character of life as a whole; • is the gap between the patient's expectations and achievements; • represents the functional effect of an illness and its consequent therapy upon the patient as perceived by the patient; • is defined as an individual's overall satisfaction with life and general sense of personal well-being; • is patient perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns (Bottomley, 2002).

The most widely applicable instrument to measure the QOL in cancer patients is the EORTC QLQ-C30. This instrument allows understanding the therapeutic decision and perceptive the reality of the control cancer patients related with quality of life. It also permits to compare the evolution of the clinical cancer status objectifying the results of quality of life, of different therapeutic interventions helping to adjust the evolution of the clinical picture as contributing health quality management as well as an economic indicator (Silveira et al., 2011).

3. Traditional Chinese Medicine

Traditional Chinese Medicine (TCM) have been developed in China and are based on a tradition with more than 2,000 years old: it includes various forms of herbal medicine, acupuncture, massage (*Tuī Ná* (推拿/推拿)), exercise (*Qìgōng* (氣功/气功)), and dietary therapy ("Wikipedia," n.d.). This philosophy is based on *Yīnyángism* (the combination of Five Phases theory with *Yīn-Yáng* (陰陽/阴阳) theory, which was later absorbed by Daoism. *Yīn* and *Yáng* are ancient Chinese concepts which can be traced back to the *Shang* dynasty (商朝 (*Shāng Cháo*)) (1600–1100 BC) (Choy, 2009). They represent two abstract and complementary aspects that every phenomenon in the universe can be divided into. Primordial analogies for these aspects are the sun-facing (*Yáng*) and the shady (*Yīn*) side of a hill. Two other commonly used representational allegories *Yīn* of and *Yáng* are water and fire.

The concept of yin and *Yáng* is also applicable to the human body; for example, the upper part of the body and the back are assigned to *Yáng*, while the lower part of the body and the front are believed to have the *Yīn* character. *Yīn* and *Yáng* characterization also extends to the various body functions, and to disease symptoms (e.g., cold and heat sensations are assumed to be *Yīn* and *Yáng* symptoms, respectively) (Greten, 2013b).

Five Phases, also translated as the "Five Elements" (五行 (*Wǔ Xíng*)) theory, presumes that all phenomena of the universe and nature can be broken down into five elemental qualities represented by Wood (木 (*mù*)), Fire (火 (*huǒ*)), Earth (土 (*tǔ*)), Metal (金 (*jīn*)), and Water (水 (*shuǐ*)). Strict rules are identified to apply to the relationships between the Five Phases in terms of sequence, the acting on each other, the counteraction, all this also applied in diagnosis and therapy (Choy, 2009; Deadman, 2001; Maciocia, 2005).

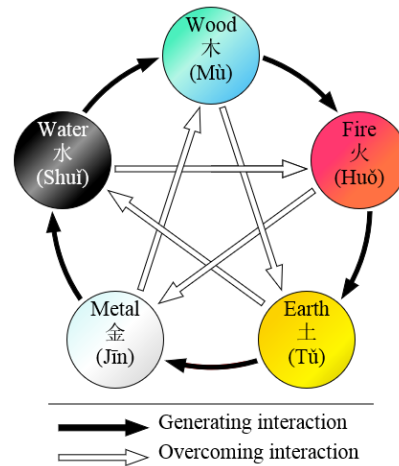


Figure 7: Compass Rose representing the five elements theory.

Source: http://upload.wikimedia.org/wikipedia/commons/thumb/f/f0/Wuxing_en.svg/652px-Wuxing_en.svg.png

https://commons.wikimedia.org/wiki/File:Wuxing_en.svg?uselang=zh

Also of the "Great Numbers" had a correspondences between the body and the universe, for example, the number of acupoints has at times been seen to be 365, corresponding with the number of days in a year; and the number of main meridians, 12 has been seen as corresponding with the number of rivers flowing through the ancient Chinese empire.

Leibniz developed the binary numbering system out of the *I Ging* (易經/易经 (*Yìjīng*)) ("The Book of Changes", the oldest book of mankind) which enables to describe circular processes, the monad. The *Yīn* and *Yáng* signs that describe this book may be considered as a mathematical expression of numbers (monad) and can be organized into bigram and trigram. Since Classical China teachings and before the Yellow Emperor's Classic of Internal Medicine (黃帝內經/黄帝内经 (*Huángdì Nèijīng*)), the regulatory fluctuations were described by circulatory functions in a simplistic manner that is similar to a sinus wave. It is part of the so-called monad (*Leibniz*) or *Tàijí* (太極/太极) sign (Greten, 2013b).

TCM believe that the body's vital energy (*Qì*) circulates through channels, that have branches connected to bodily organs and his functions such as digestion, breathing and temperature maintenance (Choy, 2009; Deadman, 2001; Maciocia, 2005).

These functions are aggregated and then associated with a primary functions such as nourishment of the tissues and maintenance of their moisture, the immune defender and temperature regulation. The entity postulated to be responsible for these are *Xuě*¹ (血) (blood); *Qì*² (vital energy), the five *Horreal* (*Zàng*³ (脏) internal organs), the six *Aulici* (*Fǔ*⁴ (腑) internal viscera), and the channels which extend through the organ systems. These are all theoretically interconnected and correlated with the idea that biological network of human regulation is organized and complex and are not linear but making part of a cyclic process that we can refer as cybernetic or regulatory model (Greten, 2013b).

According with Porkert, Chinese medicine is primarily concerned with the function, movement and vital manifestations that characterize every pathological abnormality. “Agents” are defined as factors that elicit a functional deviation and these can be exogenous (climatic or social), endogenous (emotional or constitutional factors favouring a deviation from the normal function), and neutral agents. A pathological response (“heteropathy”) is a deviation or impairment from the straight or correct direction of function (“orthopathy”) and is determined by agents of disease (Correia, 2010; Greten, 2013b).

3.1. Heidelberg Model of Chinese Medicine

Prof. Johannes Greten was a theories follower from Prof. Manfred Porkert (1974) and developed his works in medical-sinology area. The “Heidelberg model” of TCM appeared as a new scientific theory of Chinese Medicine and represents the major postulations of Chinese medicine in the western (Correia, 2010; Greten, 2013b).

A scientific system TCM is based into three preconditions: 1) Chinese Medicine should be rationally accessible; 2) Scientific evidence of the underlying mechanisms, clinical efficacy

¹ Name given to the microcirculation and blood. TCM describes such as moved structure.

² Vegetative capacity to function of a tissue or organ which may causes sensation of pressure tearing or flow.

³ Name to give in TCM for internal organs.

⁴ Name to give in TCM for internal viscera.

and general safety has to be raised and, 3) Quality control measures have to be put up on the basis of the developing knowledge of this medical system (Greten, 2013a; Pais, 2013).

Chinese Medicine was defined as “*a system of sensations and clinical signs and findings designed to define the regulatory state of the body*” (Greten, 2013a).

This model adopted a Latin terminology, supported by a binary numbering system theory from *Leibniz*. This system is based on a mathematical language used to describe biology functions in a circular movement, it's represented by a sinus wave corresponding to the cosmic movement of the seasons (spring, summer, autumn and winter). The Trigrams, representing 1/8th of the process allows to distinguish half-seasons or half-daytimes or shorter sections of the human behaviour which rhythmically occur during the day. The *Tàijí* sign means that *Yīn* and *Yáng* form a binary language of numbers that are able to describe circular functions such as regulation.

These four levels represented in the sinus wave are called guiding criteria; it describes the autonomic nervous system activity in order to systematize the diagnosis and treatment of TCM. It serves to understand the changings and regulations in the biological systems such as neurovegetative level, humorovegetative level, neuroimmunologic level and the cellular level.

This consist in vegetative regulatory process of microcirculation (“heat/cold”), defence mechanisms (theory of six stages of the *Shānghán Lùn* (傷寒論/伤寒论))) and the relation of the amount of the cell population and the respective regulatory processes (the *Yīn*, “substance”) permitting the interpretation of the symptoms that causes imbalanced processes in the body (Correia, 2010; Greten, 2013a, 2014; Oliveira, 2014; Pais, 2013).

3.2.Diagnosis according to the Heidelberg Model of TCM

The most important step in TCM is doing the correctly diagnosis. It is constituted by four parts: Constitution, Agent, Orb and Guiding Criteria.

four components of the functional diagnosis in TCM

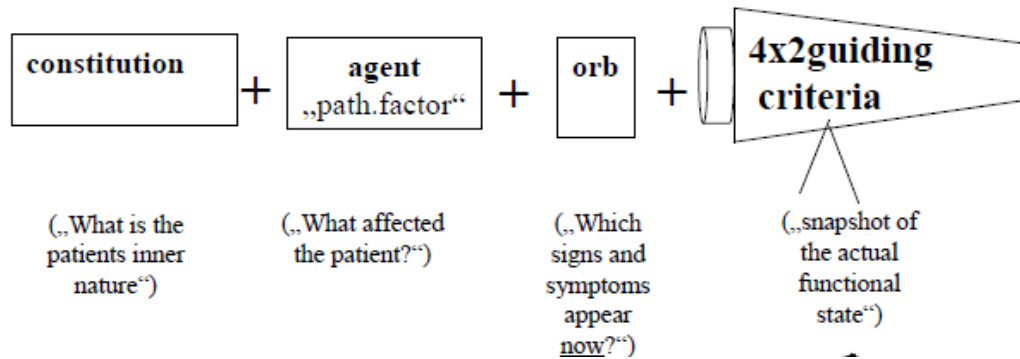


Figure 8: Schematic representation the methodology of diagnosis in TCM.

Source: (Greten, 2013b).

The **constitution** is a tendency of an individual to express the signs of one orb predominantly. It is the physical phenotype.

The **agent** is a pathogenic factor or a functional power that have the capacity to change the individual functional properties, producing clinical signs. They can be divided in external agents, internal agents and neutral agents.

The **orb** is a group of diagnostically relevant signs that indicate the functional state of a body island, which correlates with the functional properties of a conduit.

The **guiding criteria (GC)** are a regulatory model of physiology that permits the interpretation of the symptoms that are a manifestation of the body regulation.

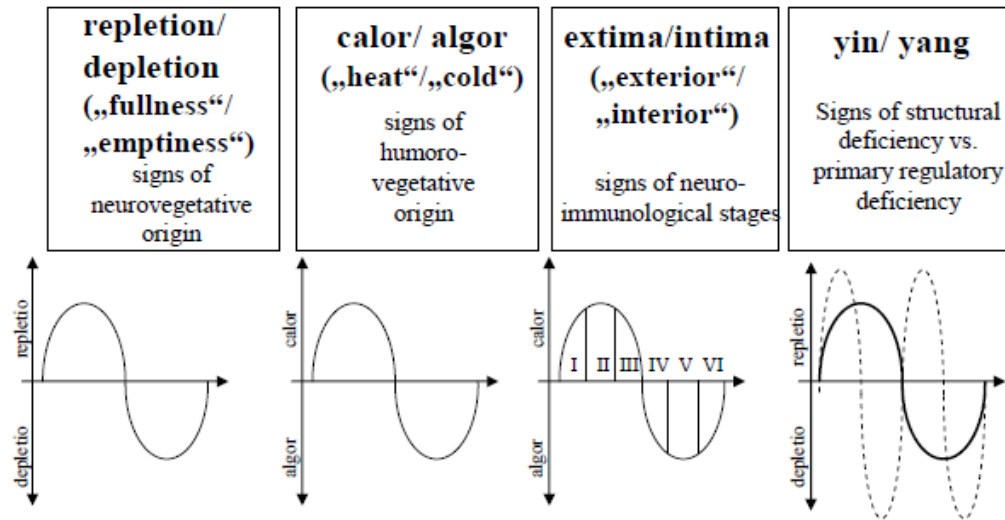


Figure 9: The Heidelberg Model of TCM.

This model establishes a parallelism between TCM concepts and physiological processes at four levels of regulation: neurovegetative, humorovegetative, neuroimmunological, and cellular level.

Source: (Greten, 2013b).

The first GC is “**repletion/depletion**” (excess/emptiness), and refers to clinical signs that have a neurovegetative origin. Repletion is similar to a relative over excitation or activating mechanism, while depletion is a lack of activation.

The second GC is “**calor/algor**” (heat/cold) and evaluates clinical signs predominantly connected with the *Xuě* (blood and circulatory system functions). These signs include: (1) the effect of microcirculation within the disease on a systemic and regional level (local interdependent mechanisms of the plasma, blood cells, endothelium, and functional tissue); (2) the activation of body fluids, evoking vegetative and systemic responses in the context of fluid distribution, fluid supply and circulation. “*Calor*” includes signs of over-activation of *Xuě* and “*Algor*” signs of a lack of functional microcirculation.

The third GC is “**extima/intima**” (exterior/interior) and evaluates signs that originate from a pathogenic factor (agent) invading the body from the exterior. *Zhāng Zhòngjǐng* (張仲景/张仲景) before the year 220 created the Treatise on Cold Damage Disorders where describe the model of the six stages of *Shānghán Lùn* or Algor Laedens Theory (ALT). According to this

theory and done a parallel with a western perspective, when “*algor*” affects the body system, it causes a regional lack of microcirculation through defence reflexes to cold, the counter-reaction (“*reactive calor*”) take place, resulting on a general increase in microcirculation, inflammation and fever.

The fourth GC is ***Yīn/Yáng*** and according to TCM, consists on the evaluation of signs that distinguish between primary deregulation (*Yáng*) and secondary deregulation due to structural deficiency (*Yīn*). In *Yīn*-diseases, symptoms are due to deficiency of the functional tissue (“body substance”, *Yīn*). *Yáng*-diseases symptoms are related with function body system problems (Correia, 2010; Greten, 2013b; Pais, 2013).

3.3.Chinese Medicine and Cancer

Traditional Chinese medicine can be a complementary and supportive care of cancer patients. This theory proposes a synergy between specific therapeutic intervention area (acupuncture, Chinese Herbs, diet, *Tuī Ná* and *Qìgōng*) based on a diagnostic (Greten, 2013b).

Combining TCM whit western practise of oncology (surgery, radiotherapy chemotherapy and pharmaceuticals) seems to have potential advantages through the synergy of biomodulation. Biomodulation means modification of tumor response and reduction of adverse effects such as modulation of immunity, prevention of cancer progression and symptom control to increase survival and to improve the quality of life (S M Sagar, 2008).

TCM recognize that the human being functions as a body-mind network. This process of body mind communication is more than rudimental structural, material and molecular view. It gives importance to the function of the small parts such as pulses of hormones neuropeptides or the electrophysiological frequency of the heart. Acupuncture stimulation in a specific point on the body releases neuropeptides (somatostatin and vasoactive intestinal peptide).within the central nervous system.

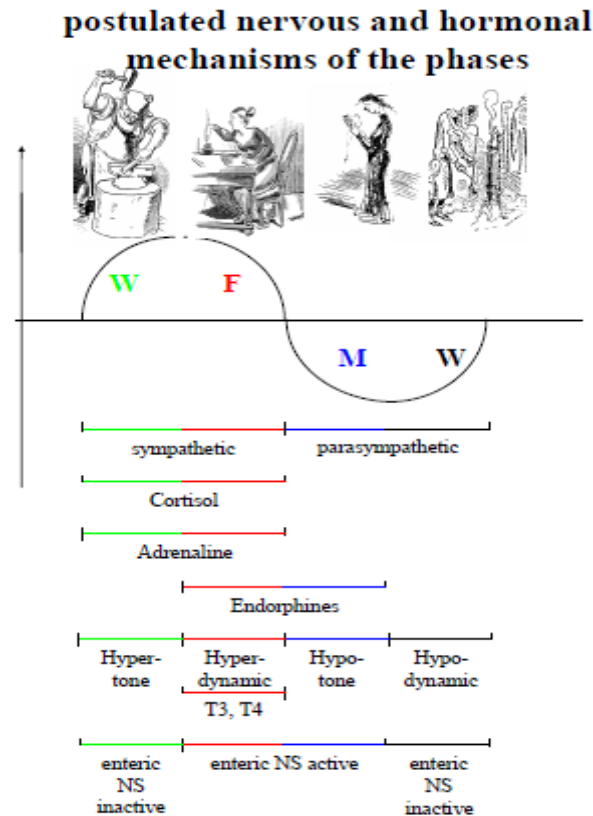


Figure 10: TCM recognize that the human being functions as a body-mind network.

Relation between the phases of Chinese medicine and autonomic nervous system with respective neurohormonal mechanisms. Source:(Greten, 2013b).

The body-mind information system is regulated by the sympathetic and parasympathetic autonomic nervous system. This corresponds to the traditional Chinese concept of a *Yīn* and *Yáng* balance which represents the relation between the structure and the function (body substance/functional system) of the *ZàngFǔ* connected by a complex and dynamical of channels where interactive information flow. When the person is healthy the communication between the systems flows freely producing a physiological interaction. So, malignant tumor is associated with stagnation of *Qì* (energy) and *Xuě* (blood). *Qì* in a Western view is an abnormality of signal transduction, cell contact and electrophysiology of cancer cells. The microcirculation within a tumor is very sluggish in some areas of the nodules and this stagnation leads poor oxygenation in the tumor (Stephen M Sagar & Wong, 2007).

In TCM cancer is associated with disturbance in information flow manifested by an excessive effect of constructive *Qì* (*Yīn* part) imbalance with the defensive *Qì* (*Yáng* part). The constructive *Qì* is comparable with the capillary flow. It is a part of *Xuě* and this function is to keep up the tissue and regenerate. *Xuě* flow is controlled by the Hepatic orb. *Defensive Qì* is a part of *extimal Qì* controlled by the pulmonary orb. This function is to dispel accumulations of *Constructive Qì* in other words not permit new neoplastic cells formation and stimulate the immune system to destroy the neoplastic cells. It describes an imbalance between the pulmonary and hepatic orb or on an emotional level this is an imbalance between sadness (*maeror*) and anger (*ira*) (Greten, 2013a).

There are scientific evidences that repressed anger with suppressed immune system can increase the risk of cancer development because the liver is under-function and it affects the movement of *Qì*. The stress can influence both function as structure of the nervous system influencing immunity a resistance to cancer (Stephen M Sagar & Wong, 2007). It is called Chinese psychosomatic theory on the origin of the cancer as a disturbed symbiosis and partnership. According with this daily life events and emotional disturbances such as partnership love, family love, suppressed autonomy, suppressed “ira” and “anger” for a prolonged period of time can induce the disease (Greten, 2013a).

Psychoneuroimmunology (PNI) studies the dynamic interaction between the mind, nervous system, endocrine system, and immunity. The interaction of emotions and immunocytes is made through neuropeptides, neurotransmitters and cytokines through electrophysiological changes in the nervous system. Interaction with the brain stem, hypothalamus, limbic system and autonomic nervous system occurs through either stimulating or suppressing the activity of afferent peripheral nerves (Lissoni et al., 2008; Stephen M Sagar & Wong, 2007).

TCM recognizes this complex interaction between personality, mood states, and susceptibility to illness through malfunction of the body-mind network. There is evidence to suggest relations between mood disorders and function of the immune system. Indeed, the experience of pain and suffering is intimately connected to immunity. A mood disorder such as helplessness and hopelessness may lead to a depressed immune system, too.

Locally the excess of *Constructive Qì* results in three stages: **stage I** the local body a type of edema or pre-edema called in MTC *humor* and *pituita* that block conduits and promote *Xuě* stasis; **stage II** is the *Congelatio* stage with an excess of palpable substance that could be accumulations of fluids such as cysts or chronic swellings with still mobility in the tissue; **stage**

III is called *Concretio* with accumulation of substances without mobility. Often is a palpable tumor which could be benign or malignant (Greten, 2013a).

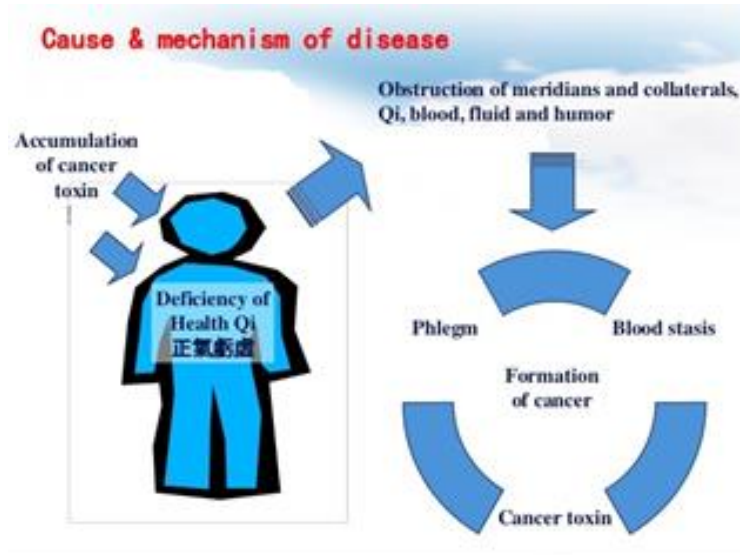


Figure 11: Mechanism of cancer disease according to MTC theory.

Source: <http://image.slidesharecdn.com/19-131016225318-phpapp02/95/19-chinese-medicine-for-side-effects-from-chemotherapy-for-colorectal-cancer-bian-zhaoxiang-7-638.jpg?cb=1381964006http://pt.slideshare.net/wilfredlin/19-chinese-medicine-for-side-effects-from-chemotherapy-for-colorectal-cancer-bian-zhaoxiang>

Other factors that reduce *defensive Qi* are *algor* and *humor*. They are *Yīn* agents reducing the effect of the energy (Greten, 2014). Some therapies such as chemotherapy and radiation lead to *Yīn* deficiency, *Xuě* deficiency, post-traumatic or toxic *algor* and swellings. It promotes symptoms of intoxication called side-effects of western therapy that MTC can help to treat to have a better functional status of systemic functions (Greten, 2013a; S M Sagar, 2008; Stephen M Sagar & Wong, 2007)

In TCM Chemotherapy is a drastic damage of the *Yīn* or the functional tissue of the body. By this strong effect some of functional tissues die by the apoptosis process. This mechanism is very efficient to destroy cancer cells but all of others healthy cells are intoxicated. Chemotherapy is considered a toxic *algor* applied intravenously so the agent *algor* (cold) is induce directly and can appear *Yáng* deficiency with ice – coldness, weakness and extreme

sensitivity to cold. This process attacks the six energy levels of ALT theory. **Stage I** *Defensive Qi* (衛氣/卫气(*Wèi Qi*)) is reduce by cold and the patient feels goosebumps, shivering and aching limbs, back pain and should pain; **Stage II** the *Qi* of the conduits is affected and there is severe pain in various regions of the body that is better by warm and worse by cold, there is a loss of appetite and nausea, swollen face and diarrhoea; **stage III** *Xuě* of conduits is affected it is transition stage before the cold enters into the intima; **stage IV** *Qi* of the orb is affected so the defence is reduced and infections of airways are frequent, general feeling of dullness; **stage V** affection of the *Xuě* of the body island and the muscles became inactive, weakness of the legs and the arms, also heart and pericardium is affected and could show serous liquids, palpitations an loss of drive; **stage VI** affection of the *Yīn* and cachexia is present, there are myalgic signs, the bones may ache, stiffness in all joints, the back is stiff and patient has problems in getting up, the muscles are weak and myalgic, urinary tract is affected, sleeplessness, brain is affected with lack of short memory (Greten, 2013a, 2014).

Cancer patients experience multiple symptoms related either side effects. Even if a patient's cancer were clinically stable, the person may still be suffering from late treatment side effects. For example, radiation may cause xerostomia, trismus and skin ulceration. These side effects have an adverse effect on quality of life, and are often not effectively managed by conventional Western medicine. MTC plays a useful role in symptom supportive care. Symptoms that can be effectively managed include general constitutional symptoms, such as fatigue and depression, pain, and specific symptoms such as gastrointestinal side effects and myelosuppression (S M Sagar, 2008; Stephen M Sagar & Wong, 2007).

Herbs from TCM have been extensively investigated in the laboratory and they have multiple pharmacologic effects. Specifying the botanical parts from which the herbal agent is prepared is important, because the active pharmacologic agents depend on their source: "*Radix*" (Rx) denotes the root; "*Cortex*" (Cx), the bark or rind; and "*Rhizome*" (Rh), the rhizome.

Many examples of anticancer therapeutic multiplicity are available: • *Rx Ginseng* has antitumor activity and inhibits platelet aggregation and induced chemotherapy immunosuppression; • *Glycyrrhizic* has antitumor activity, acts as an anti-inflammatory by increasing serum cortisol, and also increases natural killer (NK) cell activity against cancer cells. • *Rx Astragalus Membranaceus* is a powerful stimulator of the immune system, has anti-tumor activity, and inhibits platelet aggregation. • *Rx Angelica Sinensis* stimulates the immune system, has antitumor activity, inhibits platelet aggregation, and inhibits vascular permeability. • *Rh Atractylodis Macrocephala* has antitumor activity and acts as an anti-thrombotic and

fibrinolytic agent. • *Ginkgo Biloba* has multiple effects, including inhibition of platelet activation factor; stimulation of the immune system, fibrinolysis, and anti-thrombosis; scavenging of free radicals; and dilation of blood vessels to increase perfusion (Dharmananda, 1997; Greten, 2010; S M Sagar, 2008).

The TCM herbs contain a variety of chemicals that may act synergistically to inhibit tumor cell division, to increase tumor cell death (apoptosis), to increase the proportion of immune cells within the tumor, and to increase blood flow through the tumor. These changes are associated with a change in the balance of cytokines and other communicating peptides released by the immune cells, resulting in a reduction in the proliferation of tumor cells and an increase in tumor cell death, and in the minimization of many side effects for normal tissues. This synergy appears to be secondary to induction of apoptosis, anti-angiogenesis, antagonism of the viral genome, and induction of an immune response (Stephen M Sagar & Wong, 2007).

TCM also emphasizes appropriate nutrition according to specific constitutional and disease patterns. Chicken soup modulates the immune system and is preventive against airways infections (stage IV). It also serves to balance the electrolytes in diarrhoeas induced by chemotherapy, it as functions to *suppletive Yin*. This can be enriching with *Ginger*, *Curcuma* and *Ginseng*. The ginger and the temperature of the soup bring warmth into the body and detoxification. *Curcuma* detoxifies specially the hepatic orb. *R. Angelicae* can be boiled with soup for. Rice can be put into soup to harmonize the intestines.

To freely the centre of the patients that make chemotherapy we can eat: broccoli, peas, leek, spinach, red vegetables such as tomatoes and red beans, white vegetables such as celery, white beans onion and garlic (Greten, 2014).

The goals of cancer treatment should be to increase patient's survival, when possible, and to improve their quality of life. TCM is able to support patients being treated with conventional Western medicine (surgery, radiotherapy and chemotherapy) through: (1) modification of biological response to improve therapeutic gain; (2) improved psycho-neuroimmunological response; (3) enhancement of symptom control; (4) "psychospiritual" integration (Stephen M Sagar & Wong, 2007).

There is increasing evidence that suggests TCM can favourably modify the tumor physiology response to conventional Western cancer treatment. There is a correspondence between the TCM theory of cancer and recent medical research findings. TCM therapy works through more than one approach synergistical.

3.4. *Qìgōng* – An Historical Overview

Archaeological evidence suggests that the first forms of *Qìgōng* can be linked to ancient shamanic meditative practice and gymnastic exercises. Nearly 7000 year old Neolithic vessel a priest-shaman (巫覡 (*Wū Xī*)) created the essential nature which is basically the integration of the three energies of heaven, earth and man (Olga, 2013; “Qigong,” 2014).

Qìgōng appeared as a form of “remedy dancing” for health preservation. Ancient people became aware of something moving around inside their bodies such as a steam that could move up or down and in different places such as the legs or arms and connected with their breathing and the mind. The people discovered that each person had a centre just below the navel which made the rest of the body warm and strong. Gradually they realised that exist a network of conduits crossing the body connecting with the internal organs and distributed along these channels were points that communicated with the surface of the body (“Background and History of Qi-gong,” n.d., “The Origins of Qi Gong,” n.d.)

Shamanic rituals and ideas eventually evolved and formalized into Taoist beliefs and were incorporated into the field of traditional Chinese medicine (MacRitchie, 2007).

During the *Zhou* dynasty (周朝 (*Zhōu Cháo*)) the Chinese philosophical and Taoist thought came into development. There are two categories of discoveries regarding: the meditative practice and gymnastic exercises. *Lǎozǐ* (老子) wrote about breathing techniques as well as concepts such as *Yīn/Yáng* and the five elements in his book *Tao Te Jing* (道德經/道德经 (*Dàodé jīng*)) Classic on the Virtue of the *Tao* (道(*Dào*)). He advises the people to relax their heart (the chest) and to firm stomachs concentrating their minds on the centre (*Dāntián* (丹田)). The second category of gymnastic exercise is supported by writings of *Zhuāngzi* (莊子/庄子). He said: “*To blow out and breathe in slowly, to inhale and exhale, to puff out the old breaths and draw in the new, practicing bear-hanging and bird-stretching, longevity is the only concern. Guiding and pulling, cultivating and nourishing the body favoured by those who wish to live as long as Peng Zu.*” (彭祖 (*Péngzǔ*)) (Guo, 535) (“Background and History of Qi-gong,” n.d.; Lu, 1998)

The most significant developments in the history of *Qìgōng* would occur during the *Han* Dynasty (漢朝/汉朝 (*Hàn Cháo*)) (206 BC to 500 AD). The reason was the importation of the Buddhist and meditation methods from India. It began the religious *Qìgōng* time. The religious practitioners their *Qì* to a deeper level worked with internal functions of the organs and strove to control their bodies, minds and spirits in order to escape the cycle of re-incarnation.

A famous Chinese Doctor, *Huà Tuó* (華佗/华佗) (from 280-220 BC) created the “Five Animal Play” (五禽戲/五禽戏 (*Wǔqínxì*)). These techniques movements help the *Qì* flow along the channels, strengthening the body and promoting vitality. They also balance the circulation and stimulate the internal organs (“Background and History of Qi-gong,” n.d.).

During *Liang* dynasty (梁朝 (*Liáng Cháo*)) (502-557 AD) it was discovery that *Qìgōng* could be used for a martial art. Many different styles were founded such as *Taichi Nei Dan* (internal elixir) and *Shaolin Wai Dan* (external elixir) (MacRitchie, 2007).

In the *Qing* dynasty (清朝 (*Qīng Cháo*)) (1644-1911 AD) the communication between the countries such as India and Japan increased and other ways of practicing *Qìgōng* came to China.

When the cultural Revolution began (1966) most of China’s traditional culture was prohibited. All study of Taoism, Confucianism and Buddhism were destroyed and some monks and nuns were forced to abandon the religious life and only Marxism is allowed to study. Anything relating to the old way of life in China, including *Qìgōng* was condemned (Lu, 1998).

In 1978 when the Cultural Revolution end the ancient culture began to grow back. Medical workers and *Qìgōng* masters have made efforts to popularize it for health preservation and disease prevention. Scientists study *Qìgōng* in terms of physiology biochemistry and modern medicine replaced more open teaching for all people (“Background and History of Qi-gong,” n.d.).

3.5. *Qìgōng* Definition

Qìgōng is an ancient form of health maintenance dating back thousands years and an ancient Chinese psychosomatic exercise that integrates movement, breathing and meditation into a single multifaceted practise.

Greten, J, sais "*Qìgōng is the combination of two ideas. Qì (氣/气) is a vegetative capacity to function of a tissue or an organ which may cause the sensation of pressure tearing or flow and Gōng (功) is the skill of working with the Qì. Medical Qìgōng of health and healing consist in meditation, physical movements and breathing exercises*" (Greten, 2013a).

Qìgōng is a traditional form of neurovegetative biofeedback. The patient can voluntary control and have conscious about his body processes by interacting with the natural energies and integrating postural exercises, breathing movements and meditation with vegetative stabilizing properties to self-regulation the biological body systems. It is a form to stabilize body mind and spirit (Ader, 1993).

In a biomedical perspective, the *Qìgōng* causes a physiological relaxation response according to the new knowledge related on psychoneuroimmunology theory. This model reports that the effectiveness of *Qìgōng* seems to be associated with hypothalamic - pituitary response on the homeostasis sympathetic and parasympathetic of the nervous system. It contributes for the reduction of physical and emotional tension and improves the immune system. It also regulates the autonomic nervous system of blood pressure, the pupil size, the muscular activity, the pulse, the variability of heart rate and adjusts the skin and body temperature (Fong et al., 2014; M.-S. Lee, Lee, Kim, & Moon, 2003; Manzanque, Juan M, Francisca, 2004)

Qìgōng claims to foster health and healing by promoting a smooth flow of *Qì* throughout the body so that the body can heal itself (Lam, 1991).

3.6. Nowadays *Qìgōng*

Several studies were conducted at national and international levels to ascertain the physiological effects of acupuncture and *Qìgōng*.

Some experimental studies have shown that acupuncture acts on autonomic nervous system interacting with activities of the hypothalamus, spinal cord and brain cortex. For example the acupoint *Vicus Tertius Pedis* (S36 足三里 (*Zú sānlǐ*)) stimulates the activation of the hypothalamus that regulates the segregation of nitric oxide (Schwaickardt, 2013).

Electropuncture has also effects on various types of neurotransmitters that have the ability to activate enkephalinergic neurons in different regions of the brain which act on the cardiovascular activity (M. S. Lee et al., 2005).

Exploratory studies of *Qìgōng* therapy for cancer had been done in China. Chen, K. PhD reviewed more than 50 studies of *Qìgōng* therapy in clinical studies involved observation of cancer patient's self-practise, in vitro studies on laboratory-prepared cancer cells and in vivo studies on cancer-infected animal. The *Qìgōng* groups showed more improvement or had a better survival rate than conventional methods alone. In vitro studies report the inhibitory effect of *Qì* emission on cancer growth, and in vivo studies find that *Qìgōng*-treated groups have significantly reduced tumor growth (Chen & Yeung, 2002).

Oh, B. PhD made a critical review of the effects of medical *Qìgōng* (MQ) on quality of life (QOL), immune function and survival in cancer patients. The purpose of the current review was to investigate evidence for a role of one complementary and alternative medicine (CAM) in supportive care. The study involves 162 patients doing a ten week program of medical *Qìgōng*, twice a week during 90 minutes. They were also encouraged to practise at home every day for half an hour. This study concludes that MQ improve de QOL especially mood and fatigue parameters and reducing inflammation that is associated with cancer incidence and progression and survival (Oh et al., 2012).

Fong, S. PhD studied the effects of *Qìgōng* exercise in upper limb lymphedema, arterial resistance and blood flow velocity in survivors with breast cancer and mastectomy. This study is constituted by two groups: the experimental group that performed 18 forms *Tai Chi* Internal *Qìgōng* and the control group which only did a sitting position. The conclusion was that affected upper arm, elbow, forearm and wrist decreased after *Qìgōng* exercise. In terms of vascular outcomes, the resistance index decreased and the maximum systolic arterial blood flow velocity

and minimum diastolic arterial blood flow velocity increased significantly too after *Qigong* exercise. So *Qigong* could reduce conventional cancer therapy side effects such as upper limb lymphedema and poor circulatory status in survivors of breast cancer (Fong et al., 2014).

Wang, R. et al. studied the effects of *Tai Chi Chuan* (太極拳/太极拳 (*Tàijí quán*)) exercises on decreases of type 2 cytokine producing cells in postsurgical non-small cell lung cancer survivors. *Tai Chi* and *Qigong* has an effect on the balance between cellular and humoral immunity which potentiates human immunity against tumors as already said. This study concludes that a 16 week *Tai Chi* exercises diminished significantly the magnitude of the T1/T2 cytokine ratio in a population with non-small cell lung cancer survivors (Wang, Liu, Chen, & Yu, 2013).

Sprod, L. in their experience studies the relation between breast cancer survivor, health-related quality of life and biomarkers in patients doing *Tai Chi* exercises. She concluded that *Tai Chi* improve the quality of life by regulating inflammatory responses and biomarkers associated with side effects from cancer and its treatment (Sprod et al., 2012).

Another author Irwin, MR. studied also the relation between *Tai Chi* and cellular inflammation related with insomnia in breast cancer survivors. He also verified that 3 months after doing *Tai Chi* the patients reduced systemic cellular inflammatory responses and reduce the expression of genes encoding proinflammatory mediators as compared with cognitive behavioural therapy for insomnia (CBT-I) (Irwin et al., 2014)

Many others clinical reviews have been done about therapeutic benefits of *Qigong*. An interesting paper reviews was done covering medical applications scientific and experimental studies from China, USA and Europe (between 1986 and 1994) correlating *Qigong* and Drugs. Taken together these studies suggest that practicing *Qigong* exercises favourably affect many functions of the body, permit reduction of the dosage of the drugs for healthy maintenance. For hypertensive patients, combining drugs therapy and *Qigong* resulted in reduced incidence of stroke mortality and reduced dosage of the drugs required for blood pressure. For asthma patients, the combination therapy permitted reduction in drug dosage, the need for sick leave, duration of hospitalization and costs of therapy. For cancer patients, the combination therapy reduces the side effects of cancer therapy. *Qigong* also helps to rehabilitate drug addicts.

Some of this clinical studies are important to show (Sancier, 1999):

- Xu Hefen and colleagues studied changes in the immunological functions of patients who practice *Qigōng* (Xu and Qi, 1988, 1989). They compared the effects of practicing or not practicing *Qigōng* for patients with malignant tumors versus healthy people by assessing their immune activity and function (T-lymphocyte count, serum immuno-protein production (IgG, IgA, and IgM) leukocyte adherence inhibition (LAI) tests, and active E rosette formation (Ea) tests). The values for T-lymphocytes were observed to be higher for subjects who practiced *Qigōng* exercise than those that did not, whether healthy subjects or patients with tumors.
- Sun and Zhao conducted a clinical study of *Qigōng* exercise as a therapeutic aid for patients diagnosed with advanced cancer (Sun and Zhao, 1988), showing improvements (four to nine times greater than the control group) in strength, appetite, being free of diarrhoea, and weight gain of 3 kg. The phagocytic rate, a measure of the immune function, increased in the group practicing *Qigōng* but decreased in the control group.
- Wang and colleagues advised their cancer patients to persist in long-term *Qigōng* exercises during routine treatments such as chemotherapy, radiotherapy and surgery (Wang, Wang. Shao and Li, 1993). Their findings revealed that the general health of the *Qigōng* group improved with most of them having a stable or slightly declining white blood count, and chemotherapy was suspended among 92% of this group (suggesting cancer had been controlled in these patients). The general health of the control group deteriorated with a decline in white blood cell count, and chemotherapy was suspended for only 61%.
- In another study, patients with gastrointestinal tumors were divided into a group practicing *Qigōng* and a control group (Peng et al., 1989). Patients in both groups were treated appropriately with surgery, chemotherapy, radiotherapy and Chinese herbal medicine. Among those practicing *Qigōng*, the functions of the stomach and intestines improved as evidenced by an increase over the control group in the patients' appetite, white blood cell count (to normal), and survival rates (80% vs. 65% after three years, and 45% vs. 30% after five years, respectively).
- In 1993, Fu studied the effects of *Qigōng* exercises on patients with gastric carcinoma who lost the chance for an operation because of their advanced age, weakness or because their disease was in an advanced stage at first presentation. Patients were divided into a group practicing *Qigōng* and a control

group, and both groups received the anti-cancer Chinese herbal drug “*Weiliuping*.” The results showed that *Qigōng* exercise may help to promote health since the group practicing *Qigōng* improved more than the control group in relief of symptoms and in the index of immunity.

- Cong and colleagues reported the effects of *Qigōng* exercises on patients suffering from medium-late staged esophageal cancer by supplementing their combination therapy of Chinese herbs (*Tiānxiān* (天仙) capsules), radiotherapy and/or chemotherapy (Cong et al., 1996) with *Qigōng*. Results showed that practicing *Qigōng* most likely increased the therapeutic effect, decreased side effects, and improved the quality of life.

Studies have shown that those who engage in regular, moderate exercise such as brisk walking, dancing, and skating are at a lower risk of developing colorectal cancer than those who are inactive. Those with higher levels of activity, i.e. more intense/vigorous exercise for a longer duration, can reduce risk even further. Vigorous exercise includes running, cycling, aerobics, and jumping rope. Exercise is thought to lower colorectal cancer risk in part by preventing/reducing excess body weight, another risk factor for colorectal cancer and regulating hormones. The colon acts to recycles the materials in your body and store the waste for disposal. The longer waste sits in the colon or rectum, the longer toxic materials have to leach out of the solidifying stool and back into your tissues. Exercise gets your body moving, which helps move the waste in your body. This is because exercise stimulates peristalsis, a wave-like muscular contraction that helps push waste through the colon. For adults, it is recommended to get at least 30 minutes of moderate activity. People can reduce their risk by increasing physical activity in their daily lives. This can be accomplished by choosing a distant parking space, taking the stairs, shopping, cleaning, going for walks, playing with children or pets, and a multitude of other common activities. Therefore, making an effort to find a fun, physical pastime in the absence of forced intentional exercise is encouraged and can be just as equally rewarding (Meyerhardt et al., 2006).

Ortega, E. studied that inactivity increases the possibility of some cancers appears such as CRC. It has been proven that physical exercise promotes activation of immunologic system with decreased tumor growth. However are only recommended exercises from moderate to mild intensity (Ortega, Peters, Barriga, & Lötzerich, n.d.).

Prestes, J. verified the effects of five consecutive exercises sessions o leukocytes and lymphocytes count and seric cytokines levels in rats. It was concluded that low or moderate

intensities of exercise induce leucocytosis, lymphocytes and decrease in tissue lymphocytes. It also promotes decrease on TNF- α circulating levels what which means reducing inflammation process (Prestes, Dias, & Palanch, 2008).

Manzaneque, J studied the effects of *Qìgōng* practise on serum cytokines, mood and subjective sleep quality. The participants underwent training for one month. Blood samples for the quantification of TNF- α and IFN- γ and several instruments to assess anxiety and depression symptoms. This study show that *Qìgōng* practise for one month not alter serum cytokines but it enhanced psychological well-being including sleep duration (Manzaneque et al., 2009).

The practice of *Qìgōng* can be divided into two main categories: medical and martial. This study is devoted to the medical *Qìgōng* and the exercises used in this protocol are called Happy *Qìgōng*.

A summary of current scientific literature on the topic of *Qìgōng* and cancer/ immunity is listed in table 3.

Author	Date	Place	Title	Parameters/ Methodology	Results/ Conclusion
Q, Sun	1988	China	<i>Clinical observations of Qigōng as a therapeutic aid for advanced cancer patients</i>	Qigōng exercise	patients diagnosed with advanced cancer increasing the strength, the appetite, being free of diarrhoea, and weight gain of 3 kg. The phagocytic rate increased in the group practicing Qigōng and decreased in the control group.
H. Xu	1989	China	<i>Preliminary Study on Qigōng and immunity</i>	Group practicing Qigōng/ Group not practicing Qigōng in patients with malignant tumors versus healthy people	T-lymphocytes, IgG, LAI, and Ea were higher for subjects who practiced Qigōng exercise than those that did not, in both groups healthy subjects or patients with tumors.
Z. Peng	1989	China	<i>Clinical observation of 20 patients with malignant gastrointestinal tumors treated by supplementary Qigōng</i>	Group practicing Qigōng and a control group	Qigōng group, the functions of the stomach and intestines improved as evidenced by an increase in the patients' appetite, white blood cell count, and survival rates.
J. Fu	1993	China	<i>Treatment of advanced gastric cancer in the aged by the combination of Qigōng and medicinal herbs</i>	Patients were divided into a group practicing Qigōng and a control group, and both groups received the anti-cancer Chinese herbal drug "Weiliuping"	Results showed that Qigōng exercise may help to promote health since the group practicing Qigōng improved more than the control group in relief of symptoms and in the index of immunity.
S. Wang	1993	China	<i>Clinical study of the routine treatment of cancer coordinated by Qigōng</i>	Qigōng exercises during routine treatments such as chemotherapy, radiotherapy and surgery	Qigōng group improved with most of them having a stable or slightly declining white blood count, and chemotherapy was suspended among 92% of this group.
J. Cong	1996	China	<i>Clinical study on the treatment of medium-late staged esophageal cancer by Chinese-Western medicine and Qigōng therapy</i>	Qigōng exercises on patients suffering from medium-late staged esophageal cancer by supplementing their combination therapy of Chinese herbs (Tianxian capsules),	Results showed that practicing Qigōng most likely increased the therapeutic effect, decreased side effects, and improved the quality of life

				radiotherapy and/or chemotherapy	
E. Ortega	1998	Brasil	<i>A atividade física reduz o risco de câncer?</i>	Low or moderate intensity exercises	Physical exercise promotes activation of immunologic system with decreased tumor growth.
Sancier	1999	China, U.S.A., Europe	Therapeutic benefits of Qigōng exercises in combination with drugs.	Qigōng exercises	<ul style="list-style-type: none"> - reduction of the dosage of the drugs - for hypertension reduced incidence of stroke and reduced dosage of the drugs required for blood pressure. - For asthma reduction in drug dosage and duration of hospitalization and costs of therapy. - For cancer reduces the side effects of cancer therapy.
K. Chen	2002	China	<i>Exploratory studies of Qigōng therapy for cancer in China</i>	Qigōng therapy	Qigōng treated group reduced tumor growth.
M. Lee	2005	Republic of Korea	<i>Nonlinear analysis of heart rate variability during Qi therapy</i>	Electropuncture	Activate enkephalinergic neurons in different regions of the brain which act on the cardiovascular activity.
J. Prestes	2008	Brasil	<i>Influência do exercício físico em diferentes intensidades sobre o número de leucócitos, linfócitos e citocinas circulantes.</i>	Low or moderate intensity exercises	Low or moderate intensity exercises induce leucocytosis, lymphocytes and decrease in tissue lymphocytes. It also promotes decrease on TNF- α circulating levels what which means reducing inflammation process.
J. Manzanque	2009	Malaga, Spain	<i>Assessment of immunological parameters following a Qigōng training program</i>	Qigōng practise 1 month	Qigōng practice not alter serum cytokines but it enhanced psychological well-being including sleep duration.
B. Oh	2012	Sydney, Australia	<i>A critical review of the effects of medical Qigōng on quality of life, immune function, and survival in cancer patients</i>	Medical Qigōng 2x week/90 minutes	MQ improved QOL reducing mood, fatigue and inflammatory parameters.
L. Sprod	2012	Rochester, U.S.A.	<i>Health-related quality of life and biomarkers in breast cancer survivors participating in tai chi chuan</i>	Tai Chi exercises	Tai Chi improve the quality of life by regulating inflammatory responses and biomarkers associated with cancer` side effects.
A. Schwaickhardt	2013		<i>A acupuntura regula o sistema nervoso</i>	acupoint S36	activation of the hypothalamus that regulates the segregation of nitric oxide
R. Wang	2013	Shanghai, China	<i>Regular tai chi exercise decreases the percentage of type 2 cytokine-producing cells in</i>	Tai Chi exercises 16 weeks	Tai Chi exercises diminished the T1/T2 cytokines in patients with non-small cell lung cancer

			<i>postsurgical non-small cell lung cancer survivors</i>		
I. Pais	2013	Portugal	<i>Efeito da acupuntura nas células NK em doente com cancro colorectal submetidos a quimioterapia</i>	<i>acupuncture/moxa LI4, TB5, SP9, Lv3, St36, GB39, PC5 and Lu7 (8 sessions/month)</i>	<i>The study confirm an improvement in immune status and more specifically in NK cells</i>
S. Fong	2014	Hong Kong China	<i>Effects of Qigōng exercise on upper limb lymphedema and blood flow in survivors of breast cancer: a pilot study</i>	<i>18 forms of Tai Chi Internal Qigōng</i>	<i>Qigōng reduced side effects of cancer therapy such as upper limb lymphedema and poor circulatory status.</i>
M. Irwin	2014	Los Angeles	<i>Tai chi, cellular inflammation, and transcriptome dynamics in breast cancer survivors with insomnia: a randomized controlled trial</i>	<i>Tai Chi 3 months</i>	<i>reduced systemic cellular inflammatory responses and reduce the expression of genes encoding proinflammatory mediators.</i>
M. Faria	2014	Portugal	<i>Efeito da acupuntura nas células NK em doentes com cancro da mama submetidos a quimioterapia neoadjuvante a adjuvante</i>	<i>IC4; Tk5; Pc5 and P7; L3; H3; S36; F39 S32; IT6; Tk5; Rs6 with moxibustion (10 treatments, twice a week)</i>	<i>Patients with early-stage breast cancer showed a slight increase or maintenance of leukocytes, a slight increase in T and B lymphocytes and no increase in number of NK cells. Patients with breast cancer in stage IIIB, there has been no improvement on the values of all blood parameters analyzed.</i>

Table 4: Summary of research on cancer disease and *Qigōng* therapy.

Chapter II – Study Methodology

1-Study design

1.1 Investigation question and aim of the study

Investigation question:

To evaluate the effect of *Qigōng* in the immune system, in particular NK cells and on quality of life of patients with CRC.

Aim of the study:

- Assess the potential of *Qigōng* as a therapeutic method increasing the immune system function and influence the autonomic nervous system acting with sympathy and parassimphy.
- Identify the *Qigōng* exercises how it influences in the decreases the side effects of chemotherapy and the indices of stress and anxiety.

1.2.Objectives

- 1) Evaluate the effects of *Qigōng* in NK cells.
- 2) Evaluate the effects of *Qigōng* in anxiety and depression.
- 3) Evaluate the effect of *Qigōng* in quality of life for patients.
- 4) To correlate the effect of *Qigōng* in NK cells with quality of life as well as the levels of anxiety and depression of patients with CCR .
- 5) Correlate the influence of *Qigōng* with variations on the NK cells CD 56 bright and NK cells CD 56 Dim.

1.3.Hypothesis of study

Hypothesis 1: *Qìgōng* exercise has a positive effect on the number of NK cells, T and B lymphocytes in patients with CCR under chemotherapy treatment.

Hypothesis 2: *Qìgōng* improves the levels of anxiety and depression in patients with CCR under chemotherapy treatment.

Hypothesis 3: The practice of *Qìgōng* improves the quality of life of these patients.

Hypothesis 4: There is a positive correlation between objective changes in immune parameters and quality of life, depression and anxiety level.

Hypothesis 5: *Qìgōng* exercise has a effect on the number of NK cells CD 56 bright or/and NK cells CD 56 Dim.

2.Methods

A Proof of Concept study, with three study arms (verum intervention versus sham intervention versus control).

For this study we develop a Prospective, randomized, controlled, blinded study.

2.1.Recruitment

Patients will be recruited in the Oncology Service on Centro Hospitalar do Porto – Hospital de S. António.

2.1.1.Inclusion criteria

The conditions for inclusion in this study were: patients diagnosed with colorectal cancer, with regional disease and/or locally advanced disease - stages II and III and subjected to post-surgical chemotherapy.

Patients` age >18 years old and being able to give informed consent.

2.1.2.Exclusion criteria

Patients who use Colony Stimulating Factors (CSF).

Patients with poorly healed scars and without conditions to do exercise movements.

Patients that manifest symptoms of psychological disorder that cannot sign the informed consent.

3.Measurements

3.1.Main parameters

The following cellular components are: leukocyte, neutrophil, total lymphocytes, T and B lymphocytes, NK cells total; NK CD 56 bright; NK CD 56 Dim and they will be quantified in all patients of the study.

The analyses necessities to the study will be held at Cytometry Laboratory in the Unidade de Imunologia on Centro Hospitalar do Porto.

3.2.Secondary endpoints

- Socio-demographic and clinical questionnaire - The sample will be characterized on the basis of socio-demographic and clinical questionnaire including sociodemographic variables (gender, age, occupation, educational level, marital status, area of residence, current employment status, religion and household) and clinical variables (clinical diagnosis, time since diagnosis and medical treatment).

- Hospital Anxiety and Depression Scales" (HADS) - In order to evaluate the levels of anxiety and depression as well as quality of life of patients instruments are used: "Hospital Anxiety and Depression Scales" (HADS), Portuguese version validated by Pais Ribeiro et al (J. Pais Ribeiro et al, 2007). Scale developed by Zigmond e Snaith (1994), in order to assess levels of anxiety and depression in patients with physical disorders and outpatient treatment. This scale is constituted by a questionnaire that takes little time to respond. It consists of 14

items which are divided into two subscales: anxiety (7 items) and depression (7 items). The items reflect a generalized state of anxiety effects of the disease and the items of depression are associated with an anhedonia state. The response options vary between zero and three, on a scale of Likert constituted by four points. The values that are between 0 and 7 indicate absence of depression or anxiety; between 8 and 10 suggest the presence of one of its psychological states; values between 11 and 14 mean anxiety or mild depression and values between 15 and 21 are indicative of a high gravity (Pais-Ribeiro et al., 2007).

- “European Organization for Research and Treatment of Cancer Quality of Life Questionnaire” (EORTC QLQ 30). - This is an instrument created by European Organization for Research and Treatment of Cancer Quality of Life. QLQ-C30. It aims to assess relevant to any cancer patient regardless of neoplasia to assess not responding to the specific situation in each type of cancer. It consists of five functional scales (physical, performance, cognitive, emotional and social); three symptoms scales (fatigue, pain, nausea and vomiting); global health status six simple items to assess symptoms or additional problems (dyspnoea, loss of appetite, insomnia, financial difficulties, constipation and diarrhoea). Items translate into worse QLQ.

3.3.Experimental protocol

All patients will participate into a pre-intervention phase. In this phase the patients will be informed about the study design and the risks of the blood collection (hematoma, infection) in order to obtain the written consent.

In T0 (first day) all of them will answer to the questionnaires and will collect a sample of blood (for evaluate leukocyte, neutrophil, total lymphocytes, T and B lymphocytes and NK cells) by a qualified professional on Centro Hospitalar do Porto.

Using a program based on excel software, the patients will be randomized in 3 groups: the true or *verum Qìgōng* group; the placebo *Qìgōng* group and the control group.

The control group will only participate in T0 procedures.

The *verum Qìgōng* group will receive the sessions of “*Happy Qìgōng*” therapy, twice a week with the guide of the study staff; Placebo group (placebo *Qìgōng*) will do a “standing” position exercise while watching a television program of their choice.

In T1 at 15th day of the study the 2nd sample blood will be collected.

In T2 at 25th day of the study the 3rd sample blood will be collected and the patients

will answer again to the same questionnaires.

3.3. Statistical analysis

Statistical analysis will be performed using SPSS version 22 for Windows.

The characterization of the sample at baseline will be made through descriptive statistics.

The results will be submitted to the adequate statistic evaluation, with a careful analysis of the variation within each group (previously and after the *Qìgōng* therapy) and also the differences between the two groups. All values with $p < 0.05$ will be considered statistically significant.

4. Intervention

This study will integrate 30 patients. Patients will be randomized in three groups: the true or *verum Qìgōng* group (n=10); the placebo *Qìgōng* group (n=10) and the control group (n=10).

4.1. *Verum* Group

The *verum Qìgōng* group will receive 6 sessions of *Qìgōng* therapy, twice a week between the chemotherapy protocol. Blood samples will be collect at baseline (T0) on the day prior to do *Qìgōng* and the following samples will be collect in the second week of doing *Qìgōng* protocol (T1) and in the end of the *Qìgōng* protocol (T2).

Verum group will receive training exercises with the “*Happy Qìgōng*” protocol.

4.2. Sham group

The placebo *Qigōng* group will do the same protocol of the *verum Qigōng* group but not doing the real form of *Qigōng*. Placebo group (placebo *Qigōng*) will consist of a “standing” position while watching a television program of their choice.

4.3. Control group

The control group only will collect the blood sampling for the study without receiving any *Qigōng* treatment.

Note: Both groups will be encouraged to repeat the exercises daily at home. Interviews twice a week revealed that the exercise frequency was statistically equal in both groups.

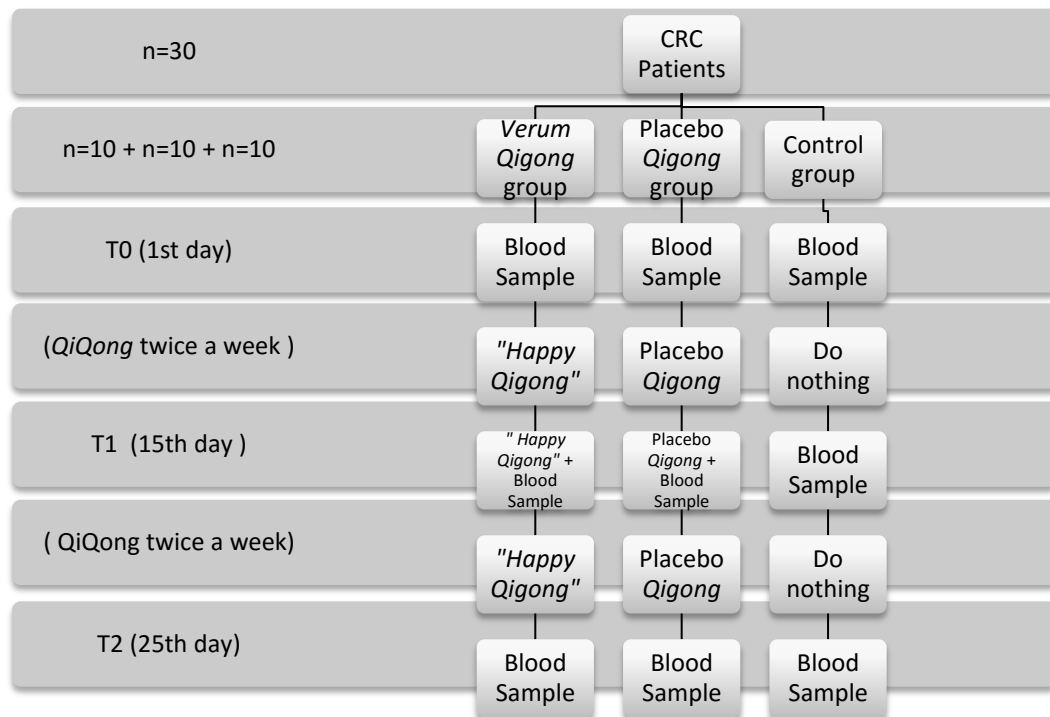


Table 5: Experiment flow-chart.

5. Qìgōng exercises and their explanation

According to Heidelberg Model of Chinese Medicine, *Qìgōng* allows the practitioner being more psychosomatically balanced by using the imagination, the motion and breathing-control. This process of subconscious self-regulation is programmed and learned. By a certain time, this balanced state may be neurologically conditioned, and remains in our vegetative nervous system, becomes part of our inner nature. The practitioner of *Qìgōng* will become more stable with challenge, resulting in a better quality of life (Duarte, 2013; Greten, 2013a).

Psychoneuroimmunology is the study of the relationship between the mind, or psychological processes, and the nervous and immune systems. The meditation component of *Qìgōng* is an example of a "psychological process" that affects physical health and well-being. The moving meditation of *Qìgōng* lowers stress, strengthens the immune system, reduces chronic inflammation, and improves cellular metabolism and aging. timeless healing *Qìgōng* can be considered a "mind-body" practice or "mind-body medicine. The idea that the mind can heal is not new. In the early 1950's Norman Vincent Peale wrote *The Power of Positive Thinking*. Peale's basic message was that individuals have the power to make themselves sick or well by their thoughts. Since 50's to 80's there are many studies in neuroscience and the psychoneuroimmunology was one result that mind-body healing is helped through laughter. Laughter therapy is widely accepted today even though it's mechanism of action is not fully understood ("The Qigong Institut," n.d.).

The selection of *Qìgōng* exercises to do in this study is called "*Happy Qìgōng*" and its main aspects are described below:

Happy Qìgōng (Qìgōng for happy life)

All the exercises should be done in a series of eight sequences.

First sequence of exercises:

MAN BETWEEN HEAVEN AND EARTH



Figure 12: Representative scheme of the Man between heaven and earth.

Source: Costa, 2015

- Put your back straight.
- Adjust your knees in order to feel the plumb line of your body through about the point *Fons Scatens* (R1涌泉 (Yǒng quán)) located on the sole of your foot.



Figure 13: R1 point (*Fons Scatens*).

Source: Porket & Hempen (1995:303).

- Through about *Conventus Omnium Yang* (Rg20 百會 (Bǎi huì)), located on the top of your head and connect with the plumb line and feel the prolongation of this inner axis towards the centre of the earth.
- Check the connection of *Conventus Omnium Yang* (Rg20) with *Fons Scatens* (R1).
- Check the connection to the earth before feeling the upward prolongation of the axis directed to the sky.

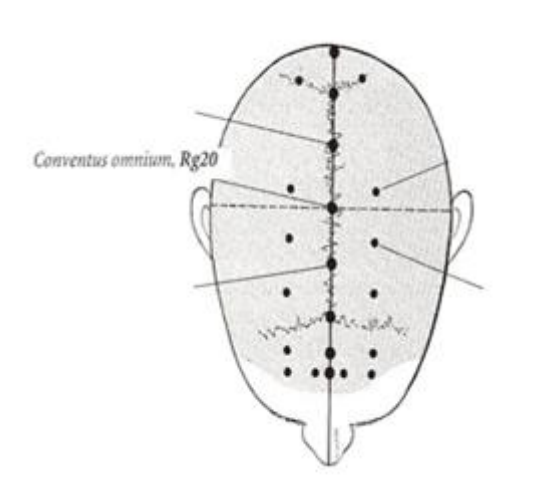


Figure 14: Rg20 Point (*Conventus Omnium Yang*).

Source: Porket & Hempen (1995:404).

BREATHING OUT 36 TIMES

- Breathing 9 times for your chest.
- Breathing 9 times for your shoulders.
- Breathing 9 times for your back vertebra.
- Breathe 1 time on each back vertebra going down to the sacred area.

HAPPY SITUATION

- Relax all of your body cells and think about a very happy situation that happened in your life.

- Imagine these feeling entering in your mind and expanding throughout in all body.

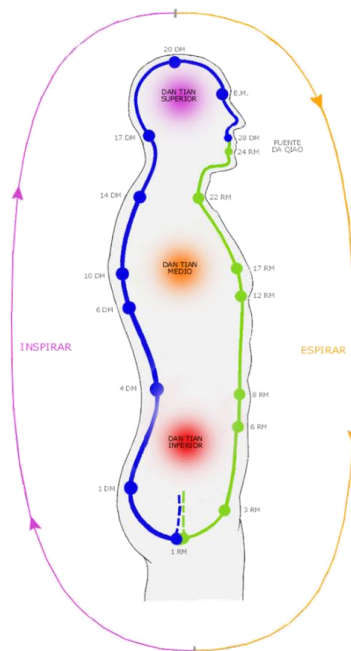


Figure 15: Energy circulation model in the body.

Source: <https://s-media-cache-ak0.pinimg.com/736x/80/dc/4d/80dc4d5affa9a6fa0ea143b350ce1b58.jpg>

WHITE BALL



Figure 16: Representative scheme of the White ball.

Source: Costa, 2015.

- Hold your arms in the form of an arch.
- Adjust the distance between your hands.
- Breathe out 7 (for boys) or 8 (for girls) times and feel the enhancement of flow between them.

Second sequence of exercises:

CONNECTING WITH SKY

ROLLING THE SHOULDERS

THE OLD MAN WHO IS IN FRONT OF THE SEA TO TAKE THE EMPTY NET FISH

TURN THE BALL

PUMP

EARTHQUAKE

GET CLARITY FROM HEAVEN

HORSE

6. Ethical Consideration

The study will be conducted in accordance with the Helsinki Declaration of 1964 and international standards of "Good Clinical Practice"

The study will be conducted with the assent of Ethics Committee from Hospital S. António of Porto.

The principles of the participant's identity will be respected (not to disclose information and avoid using political or personal information); It will be respect the subjects (questioners and results of blood tests); and to have authenticity when presenting the results.

All stakeholders will be integrated by his will and after signing informed consent attached.

Moreover, anonymity is assured for all participants throughout the process by assigning serial numbers to each person.

All participants will be informed about the study objectives and procedures. The participation will be completely voluntary and the withdrawal participation in the study will be respected at any time during the investigation.

The study will not constitute any risk to the health of the patients. There will be no interference in the conventional treatment plan set by the supporting medical staff (Human, 1974).

7.Expected Results

Based on previous study and theoretical considerations, this study looks for:

- Confirm an improvement in immune status and more specifically in NK cells.
- Clinical value of *Qìgōng* in treatment colon-rectal cancer patients.
- Improvement the quality of life in the patients with cancer.
- Evaluation cost-effectiveness from health-care systems.

8. Conclusion

Taken under consideration of all these investigation this study wants to confirm that, the effects of *Qìgōng* can be measure objectively by a variation in the immune system, specifically in NK cells.

Also the use of the psychological questionnaires will permit to evaluate the value of *Qìgōng* in improving the quality of life for patients.

In future it would be advisable to integrate *Qìgōng* in health system, due to the benefits of low coast without risks and allowing to reduce the side effects of cancer therapies including chemotherapy.

9. References

- Adams, E. K., Thorpe, K. E., Becker, E. R., Joski, P. J., & Flome, J. (2004). Colorectal cancer screening, 1997–1999: role of income, insurance and policy. *Preventive Medicine*, 38(5), 551–557. <http://doi.org/http://dx.doi.org/10.1016/j.ypmed.2003.12.014>
- Ader, R. (1993). PSYCHONEUROIMMUNOLOGY : conditioning and stress, 53–85.
- Ajcc. (2009). Colon and Rectum Cancer Staging, 4.
- Alici, E., & Sutlu, T. (2009). Natural killer cell-based immunotherapy in cancer: Current insights and future prospects. *Journal of Internal Medicine*, 266(2), 154–181. <http://doi.org/10.1111/j.1365-2796.2009.02121.x>
- Alves, G. J., & Palermo-Neto, J. (2007). Neuroimunomodulação: sobre o diálogo entre os sistemas nervoso e imune. *Revista Brasileira de Psiquiatria (São Paulo, Brazil : 1999)*, 29(4), 363–369. <http://doi.org/10.1590/S1516-44462006005000052>
- Background and History of Qi-gong. (n.d.). Retrieved January 1, 2015, from http://www.shen-nong.com/eng/lifestyles/chinese_qi_gong_history.html
- Barrett, J., & Le Blanc, K. (2009). Cancer chemotherapy and immune regulation. *American Journal of Immunology*, 5(1), 8–16. <http://doi.org/10.3844/ajisp.2009.8.16>
- Bottomley, A. (2002). The cancer patient and quality of life. *The Oncologist*, 7(2), 120–125. <http://doi.org/10.1634/theoncologist.7-2-120>
- Catarina, G., & Ribeiro, P. (2010). Carcinoma colo-rectal : diagnóstico e tratamento Carcinoma colo-rectal : diagnóstico e tratamento. Retrieved from [http://repositorio-aberto.up.pt/bitstream/10216/53439/2/Carcinoma colo-rectal Diagnostico e Tratamento.pdf](http://repositorio-aberto.up.pt/bitstream/10216/53439/2/Carcinoma%20colorectal%20Diagnostico%20e%20Tratamento.pdf)
- Chen, K., & Yeung, R. (2002). Exploratory studies of Qigong therapy for cancer in China. *Integrative Cancer Therapies*, 1(4), 345–370. <http://doi.org/10.1177/1534735402238187>
- Cheng, M., Chen, Y., Xiao, W., Sun, R., & Tian, Z. (2013). NK cell-based immunotherapy for malignant diseases. *Cellular & Molecular Immunology*, 10(3), 230–52. <http://doi.org/10.1038/cmi.2013.10>
- Choi, T.-Y., Lee, M. S., & Ernst, E. (2012). An Overview of Acupuncture and Moxibustion for Cancer Care (Vol. 3, pp. 1–18). http://doi.org/10.1007/978-94-007-4833-0_1
- Choy, P. (2009). *Curso de Acupuntura e Medicina Tradicional Chinesa, História da Medicina Tradicional Chinesa*. APA-D.A.
- Colorectal cancer risk factors. (2015). Retrieved from <http://www.cancercenter.com/colorectal-cancer/risk-factors/>

- Correia, N. (2010). *Effect of acupuncture on heart rate variability and other non-invasive hemodynamic parameters in patients with heart failure-a clinical research protocol*. Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto.
- Cotter, J., Lima, S., Barroso, S., Marinho, C., Moutinho, P., Rodrigues, A., ... Lobo, L. (n.d.). Rastreio endoscópico do cancro colorrectal. Experiência de dois anos. *Jornal Português de Gastrenterologia*, 15(4), 156–160. Retrieved from http://www.scielo.mec.pt/scielo.php?script=sci_arttext&pid=S0872-81782008000400003&lng=pt&nrm=iso&tlng=p
- Dahm, C. C., Keogh, R. H., Spencer, E. A., Greenwood, D. C., Key, T. J., Fentiman, I. S., ... Rodwell, S. A. (2010). Dietary fiber and colorectal cancer risk: A nested case-control study using food diaries. *Journal of the National Cancer Institute*, 102(9), 614–626. <http://doi.org/10.1093/jnci/djq092>
- Daniel-ribeiro, C. T., & Martins, Y. C. (2009). JORNADA FLUMINENSE SOBRE COGNIÇÃO IMUNE E NEURAL História da imunologia cognitiva. In J.-L. Peytavin (Ed.), *neurociências*. São Paulo-Brasil: Atlântida Editora.
- Deadman, P. (2001). *Manual of Acupuncture*. England.
- Dharmananda, S. (1997). The Treatment of Gastro-Intestinal Cancers with Chinese Medicine. Retrieved January 1, 2015, from <http://www.itmonline.org/arts/gicancer.htm>
- Duarte, L. (2013). *THE INFLUENCE OF QIGONG ON ADOLESCENTS ` ATTENTION : A Prospective Randomized Placebo Controlled Trial Dissertação de Mestrado em Medicina Tradicional Chinesa LEONEL JOSÉ MARQUES DUARTE THE INFLUENCE OF QIGONG ON ADOLESCENTS ` ATTENTION : Afiliação – Heid*. Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto.
- Esteves Alves do Forno, S., Castro Poças, F., & Gomes Domingues dos Santos Matos, M. E. (2012). O cancro colorretal e o rastreio: conhecimentos e atitudes dos portuenses. *GE Jornal Português de Gastrenterologia*, 19(3), 118–125. <http://doi.org/10.1016/j.jpg.2012.04.010>
- Faria, M. (2014). *EFEITO DA ACUPUNTURA NAS CÉLULAS NK EM DOENTES COM CANCRO DA MAMA SUBMETIDAS A QUIMIOTERAPIA NEOADJUVANTE E ADJUVANTE ESTUDO PROSPETIVO, RANDOMIZADO E CONTROLADO*. Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto.
- Ferlay, J., Shin, H. R., Bray, F., Forman, D., Mathers, C., & Parkin, D. M. (2010). Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *International Journal of Cancer*, 127(12), 2893–2917. <http://doi.org/10.1002/ijc.25516>
- Fernandes Jr., A., Lima, A., Lima, E., Horta, H., Coutinho, L., Martins, S., & Souza, T. (2011). Câncer de Cólon: Tratamento Quimioterápico, 1–24.
- Florea, A.-M., & Büsselberg, D. (2011). Cisplatin as an anti-tumor drug: cellular mechanisms of activity, drug resistance and induced side effects. *Cancers*, 3(1), 1351–71. <http://doi.org/10.3390/cancers3011351>

- Fong, S. S. M., Ng, S. S. M., Luk, W. S., Chung, J. W. Y., Ho, J. S. C., Ying, M., & Ma, A. W. W. (2014). Effects of qigong exercise on upper limb lymphedema and blood flow in survivors of breast cancer: a pilot study. *Integrative Cancer Therapies*, 13(1), 54–61. <http://doi.org/10.1177/1534735413490797>
- George, F. H. M. (2013). Francisco Henrique Moura George. *Norma Da Direção - Geral Da Saúde*, 9. Retrieved from <http://www.dgs.pt/upload/membro.id/ficheiros/i018596.pdf>
- Greten, H. J. (2010). *Understanding Chinese Pharmacology, Scientific Chinese Medicine, The Heidelberg Model* (4th ed.). Heidelberg School Editions.
- Greten, H. J. (2013a). *Clinical Subjects, Scientific Chinese Medicine - The Heidelberg Model* (Heidelberg).
- Greten, H. J. (2013b). *Understanding TCM, The Fundamentals of Chinese Medicine, Part I.* (H. S. Editions, Ed.) (6th ed.).
- Greten, H. J. (2014). *Understanding TCM, The Fundamentals of Chinese Medicine, Part II.* (H. S. Edition, Ed.) (6th ed.).
- Holt, P. R., Kozuch, P., & Mewar, S. (2009). Colon cancer and the elderly: from screening to treatment in management of GI disease in the elderly. *Best Practice & Research. Clinical Gastroenterology*, 23(6), 889–907. <http://doi.org/10.1016/j.bpg.2009.10.010>
- How is colorectal cancer diagnosed? (2015). Retrieved from <http://www.cancer.org/cancer/colonandrectumcancer/detailedguide/colorectal-cancer-diagnosed>
- How is colorectal cancer staged? (2015). Retrieved from <http://www.cancer.org/cancer/colonandrectumcancer/detailedguide/colorectal-cancer-staged>
- Human, D. (1974). Declaration of Helsinki. *Lancet*, 353(1), 1418–1419. Retrieved from <http://www.wma.net/en/30publications/10policies/b3/index.html>
- Irwin, M. R., Olmstead, R., Breen, E. C., Witarama, T., Carrillo, C., Sadeghi, N., ... Cole, S. (2014). Tai chi, cellular inflammation, and transcriptome dynamics in breast cancer survivors with insomnia: a randomized controlled trial. *J Natl Cancer Inst Monogr*, 2014(50), 295–301. <http://doi.org/10.1093/jncimonographs/lgu028>
- Lam, K. C. (1991). *The way of energy. Mastering the Chinese Art of Internal strength with Chi kung exercise.*
- Lee, M. S., Rim, Y. H., Jeong, D.-M., Kim, M. K., Joo, M. C., & Shin, S. H. (2005). *Nonlinear analysis of heart rate variability during Qi therapy (external Qigong).* *The American journal of Chinese medicine* (Vol. 33).
- Lee, M.-S., Lee, M. S., Kim, H.-J., & Moon, S.-R. (2003). *Qigong reduced blood pressure and catecholamine levels of patients with essential hypertension.* *The International journal of neuroscience* (Vol. 113).

- Levy, E. M., Roberti, M. P., & Mordoh, J. (2011). Natural killer cells in human cancer: from biological functions to clinical applications. *Journal of Biomedicine & Biotechnology*, 2011, 676198. <http://doi.org/10.1155/2011/676198>
- Lissoni, P., Brivio, F., Fumagalli, L., Messina, G., Vigoré, L., Parolini, D., ... Rovelli, F. (2008). Neuroimmunomodulation in medical oncology: Application of psychoneuroimmunology with subcutaneous low-dose IL-2 and the pineal hormone melatonin in patients with untreatable metastatic solid tumors. *Anticancer Research*, 28(2 B), 1377–1381.
- Lu, M. T. N. (1998). Qigong. Retrieved January 1, 2015, from <http://www.crystalinks.com/qigong.html>
- Maciocia, G. (2005). *Foundations of Chinese Medicine: A Comprehensive Text for Acupuncturists and Herbalists 2nd edition* (2^o ed.). UK: Churchill Livingstone.
- MacRitchie, J. (2007). The Eight Extraordinary Meridians QiGong. In C. U. Press (Ed.), *Qigong Fever, Body, Science and Utopia in China* (p. 186). David A. Palmer.
- Maia, Â. (2002). Emoções E Sistema Imunológico : Um Olhar Sobre a Psiconeuroimunologia.
- Manzaneque, J. M., Vera, F. M., Rodriguez, F. M., Garcia, G. J., Leyva, L., & Blanca, M. J. (2009). Serum cytokines, mood and sleep after a qigong program: is qigong an effective psychobiological tool? *Journal of Health Psychology*, 14(1), 60–67. <http://doi.org/10.1177/1359105308097946>
- Manzaneque, Juan M, Francisca, M. V. (2004). Assessment of immunological parameters following a qigong training program.
- Melo, M., & Braga, R. (2003). DO Rastreio do cancro do cólon e do recto. *Medicina*, 471–482.
- Meyerhardt, J. A., Heseltine, D., Niedzwiecki, D., Hollis, D., Saltz, L. B., Mayer, R. J., ... Fuchs, C. S. (2006). Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer: Findings from CALGB 89803. *Journal of Clinical Oncology*, 24(22), 3535–3541. <http://doi.org/10.1200/JCO.2006.06.0863>
- Moreira, A. (n.d.). CANCRO COLO-RECTAL HEREDITÁRIO.
- Nüssler, N. C., Stange, B. J., Petzold, M., Nussler, A. K., Glanemann, M., & Guckelberger, O. (2007). Original article : Reduced NK-Cell Activity in Patients with Metastatic Colon Cancer, (January), 1–9.
- Oh, B., Butow, P., Mullan, B., Hale, A., Lee, M. S., Guo, X., & Clarke, S. (2012). A critical review of the effects of medical Qigong on quality of life, immune function, and survival in cancer patients. *Integrative Cancer Therapies*, 11(2), 101–10. <http://doi.org/10.1177/1534735411413268>
- Olga. (2013). The History of Qi Gong. Retrieved January 1, 2015, from <http://blog.modernqigong.com/the-history-of-qi-gong/>

- Oliveira, R. (2014). *Qigong na escola como método de controlo da ansiedade nos professores: estudo prospetivo randomizado com controlo placebo*. Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto.
- Ortega, E., Peters, C., Barriga, C., & Lötzerich, H. (n.d.). A atividade física reduz o risco de câncer? *Revista Brasileira de Medicina Do Esporte*, 4(3), 81–86.
<http://doi.org/10.1590/S1517-86921998000300003>
- Owen, Judith A., Punt, Jenni, Stranford, S. A. (2013). *Kuby Immunology*. (W. H. F. and Company, Ed.) *W.H. Freeman and Company*. New York (Seventh Ed).
- Pais, I. (2013). *Efeito da acupuntura nas células NK em doentes com cancro colorectal submetidos a quimioterapia- estudo prospetivo, randomizado e controlado*. Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto.
- Parham Peter. (2011). *O sistema imune*. (3th ed.). Porto Alegre: artmed.
- PONTES, L., R. O. 2006. (2010). Folha Informativa. *Registo Oncológico Regional Do Norte (2006)*.
- Prestes, J., Dias, R., & Palanch, A. C. (2008). Influência do exercício físico em diferentes intensidades sobre o número de leucócitos, linfócitos e citocinas circulantes. *Revista Brasileira de Medicina*, 65(3), 56–60.
- Qigong. (2014). Retrieved January 1, 2015, from https://en.wikipedia.org/wiki/Qigong_history
- Sagar, S. M. (2008). CHINESE MEDICINE AND BIOMODULATION IN CANCER PATIENTS Chinese medicine and biomodulation in cancer patients — Part two. *In Vitro*, 8–30.
- Sagar, S. M., & Wong, R. (2007). The Scientific Basis of Chinese Medicine and Cancer Care : A Western Medicine Perspective. *World*, 11, 1–18.
- Saikali, J., Picard, C., Freitas, M., & Holt, P. (2004). Fermented milks, probiotic cultures, and colon cancer. *Nutrition and Cancer*, 49(April 2014), 14–24.
http://doi.org/10.1207/s15327914nc4901_3
- Sancier, K. M. (1999). Therapeutic benefits of qigong exercises in combination with drugs. *Journal of Alternative and Complementary Medicine (New York, N. Y.)*, 5(4), 383–389.
<http://doi.org/10.1089/acm.1999.5.383>
- Schwaickardt, A. M. (2013). A acupuntura regula o sistema nervoso. Retrieved January 1, 2015, from <http://agulhinhasdobem.blogspot.pt/2013/06/a-acupuntura-regula-o-sistema-nervoso.html>
- Silveira, A., Gonçalves, J., Sequeira, T., Ribeiro, C., Lopes, C., Monteiro, E., & Pimentel, F. L. (2011). Avaliação da qualidade de vida em doentes com patologia oncológica da cabeça e pescoço modelo de validação da versão electrónica Portuguesa do EORTC-QLQ C30 e EORTC- H&N35. *Acta Medica Portuguesa*, 24(SUPPL.2), 347–354.

- Sprod, L. K., Janelins, M. C., Palesh, O. G., Carroll, J. K., Heckler, C. E., Peppone, L. J., ... Mustian, K. M. (2012). Health-related quality of life and biomarkers in breast cancer survivors participating in tai chi chuan. *Journal of Cancer Survivorship*, 6(2), 146–154. <http://doi.org/10.1007/s11764-011-0205-7>
- Staging and Grading. (n.d.). Retrieved January 1, 2015, from <http://www.prostate.org.au/articleLive/pages/Staging-and-Grading.html>
- Takhar, A. S., Eremin, O., & Watson, S. A. (2004). The role of gastrin in colorectal carcinogenesis. *The Surgeon*, 2(5), 251–257. [http://doi.org/10.1016/S1479-666X\(04\)80093-3](http://doi.org/10.1016/S1479-666X(04)80093-3)
- The Origins of Qi Gong. (n.d.). Retrieved January 1, 2015, from http://www.literati-tradition.com/qi_gong_origins.html
- The Qigong Institut. (n.d.). Retrieved January 1, 2015, from <http://www.qigonginstitute.org/html/epigenetics.php>
- U.S.Department of health and human services. (2003). *understanding the immune system, How it Works*. U.S.: SCIENCE EDUCATION.
- Waldhauer, I., & Steinle, A. (2008). NK cells and cancer immunosurveillance. *Oncogene*, 27(45), 5932–5943. <http://doi.org/10.1038/onc.2008.267>
- Wang, R., Liu, J., Chen, P., & Yu, D. (2013). Regular tai chi exercise decreases the percentage of type 2 cytokine-producing cells in postsurgical non-small cell lung cancer survivors. *Cancer Nursing*, 36(4), 27–34. <http://doi.org/10.1097/NCC.0b013e318268f7d5>
- Wikipedia. (n.d.). Retrieved January 1, 2015, from https://en.wikipedia.org/wiki/Traditional_Chinese_medicine

Anexos

Folha de Identificação

Nº de identificação _____

Nome da participante _____

Contacto _____

Processo clínico nº _____

Diagnóstico _____

Data do Diagnóstico ____/____/____

Estádio _____

Data ____/____/____

Qualidade de vida em doentes com cancro do colo-rectal**Questionário Sociodemográfico e Clínico**

1. Data de Nascimento: ____/____/____ 1.1. Idade: _____

2. Nacionalidade: _____

3. Naturalidade: _____

4. Raça: _____

6. Habilitações literárias:

Sem escolaridade ☐ 4ª classe ☐ 6º ano ☐ 9º ano ☐ 12º ano ☐

Bacharelato ☐ Licenciatura ☐ Mestrado ☐ Doutoramento ☐

Outro _____

7. Profissão: _____

8. Situação Profissional:

Activo ☐ Desempregado ☐ Reformado ☐ Baixa Médica ☐

Outro _____

9. Estado Civil: Solteiro ☐ Casado ☐ União de Facto ☐

Divorciado ☐ Separado ☐ Viúvo ☐

10.1. Qual a duração da relação actual? _____

11. Tem filhos? Sim _____ Não _____ Quantos? _____

12. Na maior parte do ano reside:

Com pais ☐ Com filhos ☐ Sozinho/ a ☐

Com cônjuge/companheiro ☐

Com outros familiares (irmãos, tios, primos) ☐

Em lar ou instituição de acolhimento ☐

13. Apoio familiar

Sim ☐ Não ☐

14. Já faleceu alguém que tinha significado para si?

Sim ☐ Não ☐

14.1 Se sim indique de 1-10 a perda que significou para si _____

Relativo à doença:

1. Indique, por favor, a data na qual obteve o diagnóstico: _____

2. Como foi detectado o cancro:

Exame médico de rastreio ☐ Consulta clínica ☐

Outros _____

3. Fez quimioterapia antes da cirurgia?

Sim ☐ Não ☐

3.1. Indique, por favor, qual a fase actual do tratamento (ex. estou a terminar a quimioterapia): _____

4. Já alguma vez utilizou terapêuticas alternativas?

Sim ☐ Não ☐

4.1. Se sim, quais?

Acupunctura Naturopatia Homeopatia Fitoterapia

Outros _____

5. Este foi o seu primeiro diagnóstico de cancro do cólon rectal?

Sim ☐ Não ☐

6. Tem ou teve outra doença física?

Sim ☐ Não ☐

6.1. Se sim, qual (quais)? _____

7. Antecedentes familiares com o diagnóstico de cancro?

Sim ☐ Não ☐

7.1. Se sim, qual o grau de parentesco e qual o tipo de cancro? _____

8. Tem ou teve uma patologia psiquiátrica?

Sim ☐ Não ☐

8.1. Se sim, qual (quais)? _____

8.2. Tem ou teve acompanhamento psicológico/ psiquiátrico?

Sim ☐ Não ☐

8.3. Se sim, quando?

Antes do diagnóstico ☐ Depois do diagnóstico ☐

De seguida irá encontrar dois questionários referentes à experiência pessoal de cancro (QLQ-30) e do cancro do colo-retal (QLQ-CR29) relacionados com a qualidade de vida e outro relacionado com a ansiedade e depressão (HADS). Por favor responda a TODAS as questões.

Escala de Ansiedade e Depressão Hospitalar (HADS)

e-mail: jlpr@fpce.up.pt

Exmo. Senhor Prof. Doutor José Pais-Ribeiro,

Venho por este meio solicitar a V. Ex.^a, a autorização para a utilização da Versão Portuguesa da Escala de Ansiedade e Depressão Hospitalar. O meu nome é Sara Patrícia Carvalho Costa, sou aluna de mestrado em Medicina Tradicional Chinesa a fazer o trabalho intitulado: “Efeito do Qìgōng nas células NK em doentes com cancro do colo-retal submetidos a quimioterapia” no Centro Hospitalar de Santo António do Porto que será desenvolvido no contexto da Dissertação do Mestrado do Instituto de Ciências Biomédicas Abel Salazar, da Universidade do Porto.

O presente trabalho tem por objectivos avaliar os índices de depressão e ansiedade nos doentes oncológicos a fazer quimioterapia antes e pós serem submetidos à realização de Qìgōng. É esperado que a terapia de Qìgōng tenha um impacto positivo sobre o sistema imunológico dos doentes com CCR, nomeadamente na diferenciação das células NK, e que se verifique uma melhoria do estado psicoemocional bem como da qualidade de vida destes intervenientes.

E por conseguinte, venho pedir as referências necessárias para a cotação do mesmo.

Agradecendo desde já a sua atenção, ficamos ao seu dispor para esclarecimentos que achar pertinentes, sobre este assunto.

Com os meus melhores cumprimentos,

Sara Patrícia Carvalho Costa

Response to the authorization request.



Sara Costa <scosta78@gmail.com>

Pedido de autorização da Escala de Ansiedade e Depressão Hospitalar

José Luis Pais Ribeiro <jlpr@fpce.up.pt>
Para: Sara Costa <scosta78@gmail.com>

3 de maio de 2015 14:51

Cara colega

Não me oponho à utilização da Versão Portuguesa da Escala de Ansiedade e Depressão Hospitalar que traduzi e estudei para a população portuguesa.

Cordialmente

José Luis Pais Ribeiro
jlpr@fpce.up.pt
mobile phone: (351) 965045590
web page: <http://sites.google.com/site/jlpraisribeiro/>
ORCID: <http://orcid.org/0000-0003-2882-8056>
Lattes: <http://lattes.cnpq.br/1488255260017966>
ResearchGate: https://www.researchgate.net/profile/Jose_Pais-Ribeiro/publications

ESCALA HAD - AVALIAÇÃO DO NÍVEL DE ANSIEDADE E DEPRESSÃO

DADOS PESSOAIS			
NOME _____			
ORIENTAÇÕES PARA REALIZAÇÃO DO TESTE			
Assinale com "X" a alternativa que melhor descreve sua resposta a cada questão.			
1. Eu sinto-me tensa (o) ou contraída (o):			
() a maior parte do tempo [3]	() grande parte do tempo [2]	() de vez em quando [1]	() nunca [0]
2. Eu ainda sinto que gosto das mesmas coisas de antes:			
() sim, da mesma forma que antes [0]	() não tanto como antes [1]	() apenas um pouco [2]	() já não consigo gostar de nada [3]
3. Eu sinto uma espécie de medo, como se alguma coisa má me fosse acontecer:			
() sim, de maneira muito forte [3]	() sim, mas não tão forte [2]	() pouco, mas isso não me preocupa [1]	() não sinto nada [1]
4. Rio-me e divirto-me quando vejo coisas engraçadas:			
() da mesma maneira que antes [0]	() actualmente, um pouco menos [1]	() actualmente, bem menos [2]	() já não consigo [3]
5. Sinto muitas preocupações:			
() a maior parte do tempo [3]	() grande parte do tempo [2]	() de vez em quando [1]	() raramente [0]
6. Sinto-me alegre:			
() nunca [3]	() poucas vezes [2]	() muitas vezes [1]	() a maior parte do tempo [0]
7. Consigo ficar sentado à vontade e sentir-me relaxado:			
() sim, quase sempre [0]	() muitas vezes [1]	() poucas vezes [2]	() nunca [3]
8. Sinto-me lenta (o) a pensar e a fazer coisas:			
() quase sempre [3]	() muitas vezes [2]	() poucas vezes [1]	() nunca [0]
9. Tenho uma sensação de medo, como um frio na barriga ou um aperto no estômago:			
() nunca [0]	() de vez em quando [1]	() muitas vezes [2]	() quase sempre [3]
10. Perdi o interesse em cuidar da minha aparência:			
() completamente [3]	() não me tenho cuidado como deveria [2]	() talvez não tanto quanto antes [1]	() cuido-me da mesma forma que antes [0]
11. Sinto-me inquieta(o), como se não pudesse ficar parada(o) em lugar nenhum:			
() sim, demais [3]	() bastante [2]	() um pouco [1]	() não me sinto assim [0]
12. Fico animada(o) à espera das coisas boas que estão por vir:			
() da mesma forma que antes [0]	() um pouco menos que antes [1]	() bem menos do que antes [2]	() quase nunca [3]
13. De repente, tenho a sensação de entrar em pânico:			
() a quase todo o momento [3]	() várias vezes [2]	() de vez em quando [1]	() não sinto isso [0]
14. Consigo sentir prazer quando assisto a um bom programa de televisão, de rádio ou quando leio alguma coisa:			
() quase sempre [0]	() várias vezes [1]	() poucas vezes [2]	() quase nunca [3]
RESULTADO DO TESTE:			
OBSERVAÇÕES:			
Ansiedade: [] Questões (1,3,5,7,9,11,13)		Pontuação:	
Depressão: [] Questões (2,4,6,8,10,12 e 14)		0 – 7 pontos: improvável	
		8 – 11 pontos: possível – (questionável ou duvidosa)	
		12 – 21 pontos: provável	

Referências: Zigmond, A.S.7 Snaith, R.P. The Hospital Anxiety and Depression Scale. Acta Psychiatrica Scandinavica 1983; 67,361-370

Botega NJ, Bio MR, Zomignani MA, Garcia JR C, Pereira WAB. Transtornos do humor em enfermagem de clínica médica e validação de escala de medida (HAD) de ansiedade depressão. Revista de Saúde Pública, 29(5): 355-63, 1995.



EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

Your birthdate (Day, Month, Year):

Today's date (Day, Month, Year):

	Not at All	A Little	Quit a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a <u>long</u> walk?	1	2	3	4
3. Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quit a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4

16. Have you been constipated?	1	2	3	4
--------------------------------	---	---	---	---

During the past week:

	Not at All	A Little	Quit a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor

Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor

Excellent



EORTC OLO – CR29

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
31. Did you urinate frequently during the day?	1	2	3	4
32. Did you urinate frequently during the night?	1	2	3	4
33. Have you had any unintentional release (leakage) of urine?	1	2	3	4
34. Did you have pain when you urinated?	1	2	3	4
35. Did you have abdominal pain?	1	2	3	4
36. Did you have pain in your buttocks/anal area/rectum?	1	2	3	4
37. Did you have a bloated feeling in your abdomen?	1	2	3	4
38. Have you had blood in your stools?	1	2	3	4
39. Have you had mucus in your stools?	1	2	3	4
40. Did you have a dry mouth?	1	2	3	4
41. Have you lost hair as a result of your treatment?	1	2	3	4
42. Have you had problems with your sense of taste?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
43. Were you worried about your health in the future?	1	2	3	4
44. Have you worried about your weight?	1	2	3	4
45. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
46. Have you been feeling less feminine/masculine as a result of your disease or treatment?	1	2	3	4
47. Have you been dissatisfied with your body?	1	2	3	4
48. Do you have a stoma bag (colostomy/ileostomy)? (please circle the correct answer)	Yes		No	

During the past week:

Not at All A Little Quite a Bit Very Much

Answer these questions ONLY IF YOU HAVE A STOMA BAG, if not please continue below:

49. Have you had unintentional release of gas/flatulence from your stoma bag?	1	2	3	4
50. Have you had leakage of stools from your stoma bag?	1	2	3	4
51. Have you had sore skin around your stoma?	1	2	3	4
52. Did frequent bag changes occur during the day?	1	2	3	4
53. Did frequent bag changes occur during the night?	1	2	3	4
54. Did you feel embarrassed because of your stoma?	1	2	3	4
55. Did you have problems caring for your stoma?	1	2	3	4

Answer these questions ONLY IF YOU DO NOT HAVE A STOMA BAG:

49. Have you had unintentional release of gas/flatulence from your back passage?	1	2	3	4
50. Have you had leakage of stools from your back passage?	1	2	3	4
51. Have you had sore skin around your anal area?	1	2	3	4
52. Did frequent bowel movements occur during the day?	1	2	3	4
53. Did frequent bowel movements occur during the night?	1	2	3	4
54. Did you feel embarrassed because of your bowel movement?	1	2	3	4

During the past 4 weeks:

Not at All A Little Quite a Bit Very Much

For men only:

56. To what extent were you interested in sex?	1	2	3	4
57. Did you have difficulty getting or maintaining an erection?	1	2	3	4

For women only:

58. To what extent were you interested in sex?	1	2	3	4
59. Did you have pain or discomfort during intercourse?	1	2	3	4

INFORMAÇÃO PARA OS PARTICIPANTES:

A presente investigação tem por objectivo principal avaliar os efeitos de *Qìgōng*, uma terapia incluída no tratamento da medicina chinesa que consiste numa ginástica que usa exercícios respiratórios associados a exercícios músculo-esqueléticos, no sistema imunitário em doentes que frequentam o Hospital de Dia e se encontram a fazer tratamento de quimioterapia pós-cirurgia. Para tal, será recolhida uma amostra sanguínea pela equipa de enfermagem do serviço de Oncologia.

Em simultâneo, serão realizados questionários sócio-demográficos, de avaliação da qualidade de vida e de avaliação da ansiedade e depressão, para perceber quais as principais repercussões da doença na sua vida pessoal e familiar, bem como identificar a necessidade actual ou futura de apoio psicológico para si ou família. Também pretende avaliar a qualidade de informação que tem sobre a sua doença.

Se concordar em participar entrará num programa de ginástica respiratória, durante 3 semanas consecutivas, duas vezes por semana. Será também consultado o seu processo clínico e ser-lhe-á solicitado que responda aos questionários com o apoio da investigadora principal. Quaisquer dados relativos à identificação dos participantes neste estudo serão confidenciais e anónimos, assim como a sua divulgação, no meio científico, dos resultados obtidos. Os participantes podem recusar ou interromper, a qualquer momento, a participação no estudo sem nenhum tipo de penalização por esse facto.

Em caso de dúvidas ou perguntas relativas a este estudo poderá contactar-me. Estarei ao dispor.

Muito obrigada!

Sara Patrícia Carvalho Costa – Mestrado em Medicina Tradicional Chinesa – ICBAS/UP

TERMO DE CONSENTIMENTO INFORMADO

Efeito do *Qigōng* nas Células NK em doentes com Cancro do colo-rectal submetidos a quimioterapia.

Eu, abaixo-assinado _____

Fui informado de que o Estudo de Investigação acima mencionado se destina à realização de um estudo de investigação.

Sei que neste estudo está prevista a realização de uma análise sanguínea e realização de uma sequência de exercícios respiratórios e de movimentos corporal tendo-me sido explicado em que consistem e quais os seus possíveis efeitos.

Foi-me garantido que todos os dados relativos à identificação dos Participantes neste estudo são confidenciais e que será mantido o anonimato.

Sei que posso recusar-me a participar ou interromper a qualquer momento a participação no estudo, sem nenhum tipo de penalização por este.

Compreendi a informação que me foi dada, tive oportunidade de fazer perguntas e as minhas dúvidas foram esclarecidas.

Aceito participar de livre vontade no estudo acima mencionado.

Concordo que sejam efectuados os exames e a colheita de amostras de sangue para realizar as análises que fazem parte deste estudo.

Também autorizo a divulgação dos resultados obtidos no meio científico, garantindo o anonimato.

Nome do Participante no estudo

Data

Assinatura

____/____/____

Nome do Investigador Responsável

Data

Assinatura

____/____/____
